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HISTAMINE DERIVATIVES WITH PROLONGED ACTION

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DALE and Laidlaw in 1910 pointed out the similarity between anaphylactic shock and the physiologic action of histamine. Since the publication of their paper, there has been an ever-increasing interest by allergists in histamine, its action, and its use in treatment. Since it is not the purpose of this paper to discuss the part played by histamine in anaphylaxis or allergy, nor to consider the advisability of the use of histamine as a therapeutic agent, no attempt is being made to survey the literature; but instead, if the reader is interested in these phases, he is referred to the work and bibliographies of: Code,[2] Dragstedt,[3] Horton,[6] Sheldon,[10] Rocha e Silva,[9] and an editorial on the use of histamine.[4]

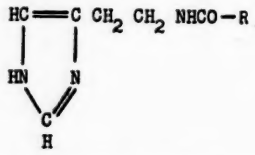
THE PROBLEM

In the therapeutic use of histamine, it has been found advisable to give several daily injections or, as Horton,[6] Sheldon,[10] and others have done, to give it by intravenous administration. The inconvenience of several doses daily or the daily administration by the intravenous method is apparent and need not be discussed. If a preparation of histamine could be made which, when injected, had but little immediate histamine action, but slowly over a period of time liberated histamine, this would simplify histamine therapy. With this in mind, a number of preparations of histamine derivatives have been prepared with the thought that in the body these compounds would be broken down and histamine liberated slowly, or that their physiological action would be less intense than histamine but of much longer duration.

EXPERIMENTAL STUDIES

Eighteen histamine derivatives have been prepared. Their structural formula, melting point (Fisher block), and immediate histamine-like

TABLE I. HISTAMINE DERIVATIVES AND THEIR ACTIONS



Compound No.	R	Melting Point	Immediate Histamine-like Action on 300-400 gm. Guinea Pigs When Injected Subcutaneously	Liberation of Histamine in Body†
RA 12	—CH_3	149	20 mg. showed no reaction	1
RA 11 B-7	—CH_2 . HCL	128	20 mg. showed no reaction	1
RA 18	—CH_2 . CH_2CH_3	127	20 mg. showed no reaction	2
RA 19	—$CH_2CH_2CH_2CH_2CH_3$	128—130	20 mg. killed in several hours	3
RA 28	—CH_2CH_2COOH	115	20 mg. no effect	0
RA 20	—NH_2	120—124	20 mg. no effect	0

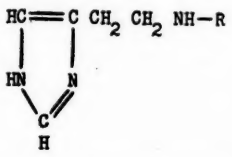
† 0 — none; 1 — very slowly; 2 — slowly; 3 — more rapidly.

action on the guinea pig and the dissociation or liberation of histamine in the body are shown in Tables I, II, and III. Liberation of histamine in the body is estimated and indicated by an arbitrary scale, as we have no accurate means of measuring this change. In the tables under this column, "0" means no liberation of histamine; "1" means slowly liberated; "2" means a little more is liberated and a little faster than indicated by the figure "1"; and "3" means still more and faster. (These figures, instead of representing liberation of histamine in the body, may represent prolonged action.)

It has been claimed that the NH_2 group is the toxic group and the NH group is the anchoring group in histamine.[7,9] Many of our compounds have the NH_2 group blocked and lose their histamine action. However, this is not true in all cases, as in compounds RA-7, RA-29 and RA-30. It will be noted that they have as much immediate histamine-like action as histamine itself. Thus, attaching a radical to the NH_2 group does not always block the histamine action, but inactivation depends somewhat on the blocking radical.

It is not easy to attach a radical to the NH group, as when this is attempted, the aminazole ring tends to rupture. However, we have succeeded in attaching a radical to the NH group as shown in compound RA-29. In this compound it has not interfered with its physiological action.

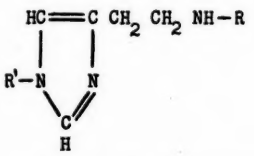
TABLE II. HISTAMINE DERIVATIVES AND THEIR ACTIONS



Compound No.	R*	Immediate Histamine-like Action on 300–400 gm. Guinea Pigs When Injected Subcutaneously	Liberation of Histamine in Body†
RA-2**	$-CH_2COOH$	10 mg. killed 50% in 30 minutes	2
RA-21	$-CH_2CO_2C_2H_5$	15 mg. gave difficult breathing but pigs survived	2
RA-8	$CH_3CH_2\underset{\vert}{C}HCOOH$	5 mg. killed 50% in several hours	—
RA-10	$CH_3CH_2CH_2\underset{\vert}{C}HCOOH$	7½ mg. killed 50%	—
RA-9	$CH_3(CH_2)_5\underset{\vert}{C}HCH_3$	2½ mg. killed in 30 minutes	—
RA-6	$-CH_2CH_2CH_2OH$	20 mg. killed in 1 hour	2

* These compounds were so hygroscopic that melting point determinations were unsatisfactory.
** The hydrochloride of this compound has also been made.
† 0 — none; 1 — very slowly; 2 — slowly; 3 — more rapidly.

TABLE III. HISTAMINE DERIVATIVES AND THEIR ACTIONS



Compound No.	R	R′	Melting Point	Immediate Histamine-like Action on 300–400 gm. Guinea Pigs When Injected Subcutaneously	Liberation of Histamine in Body†
RA-7	$-CH_3$	H	*	As or more active than histamine	—
RA-30	$-C(=NH)-NH-C(=NH)-NH_2$	$-C(=NH)-NH-C(=NH)-NH_2$	182	On basis of histamine content as active as histamine	—
RA-29	H	$-C(=NH)-NH-C(=NH)-NH_2$	188	On basis of histamine content as active as histamine	—
RA-31	$-C(=O)CH_3$	$-C(=NH)-NH-C(=NH)-NH_2$	80	20 mg. no effect	1
RA-16	$-CH_2SO_2Na$	H	Decomp.	30 mg. no effect	0—1
RA-27	$-COOC_2H_5$	H	192	5 mg. killed in 30 minutes	3

* Hygroscopic.
† 0 — none; 1 — very slowly; 2 — slowly; 3 — more rapidly.

CLINICAL STUDIES

Compounds RA-12, RA-18, RA-2, and RA-21 were tried clinically. However, RA-18 was used very little as it tended to give a local reaction. RA-2 and RA-21 were most satisfactory clinically, but their use was limited due to difficulty of preparing pure preparations. Most of the cases were treated with RA-12, N-acetyl histamine.

The initial dose for RA-18, RA-2 and RA-21 was 1 milligram. This dose was increased a milligram at a time until the maximum tolerated dose had been reached. This maximum tolerated dose for RA-2 was usually from 5 to 10 milligrams.

As stated above, the compound used most was RA-12, N-acetyl histamine. The initial dose of this compound was 5 milligrams, and this was increased 5 milligrams at a time to a maintenance dose of 20 milligrams and occasionally to 30 milligrams.

While building up the doses, they were given twice weekly. After the maintenance dose had been reached, it was given once weekly. All doses were injected subcutaneously. The preparations used were a 1 or 2 per cent solution (10 to 20 mg./c.c.) preserved with 1:10,000 merthiolate, and Seitz-filtered. All solutions were cultured to be certain that they were sterile.

Seven cases of atopic dermatitis have been treated, of which four showed marked improvement and three gave doubtful or no results. In five cases of contact dermatitis, three responded satisfactorily. Nine cases of urticaria have been treated, six of which were improved. Two cases of asthma were treated with no results whatever (one was made worse). Three cases of vasomotor rhinitis were treated with no results. Three cases of migraine were treated, with two giving excellent response. One case of infantile eczema was treated with a satisfactory response. In this one case we had a histamine-like reaction, which for a few hours gave us considerable anxiety. We treated one case of Ménière's disease with partial improvement. Two cases of drug allergy were treated, one with the acetyl compound, the other with the acetic acid compound, namely, compounds RA-12 and RA-2. The results were most gratifying. Two cases of hay fever were treated with no results.

Whether these results were coincidental could not be stated. There is need of many more cases before any conclusion can be drawn. Besides the cases reported here, Dr. Harry Rogers of Philadelphia, Dr. H. R. Hoeger of Brookville, Indiana, and Dr. Paul Moore of Muncie, Indiana, have used some of these compounds. They report results similar to ours.

DISCUSSION

The writer is inclined to agree with Horton who states, "The doctor will never know the real romance of medicine unless he has used histamine therapy." But histamine therapy by frequent subcutaneous injection,

instillation into the skin, or daily intravenous injections, is not entirely convenient or satisfactory. Therefore, if a substance could be made which, when injected, would slowly liberate histamine, then this therapy would be more simple and more available. It is possible that instead of liberating histamine slowly in the body, the results are due to the pharmacological action of these compounds. Namely, their action is not as intense as histamine and their prolonged action results because the body does not destroy them as rapidly as it does histamine. Thus, they produce a mild but prolonged histamine-like reaction.

One type of compound may be better for one disease and another for a different condition. Thus, compound RA-27, ethyl histamine carbonate, might be best suited for treatment of Ménière's disease and multiple sclerosis.

The therapeutic results of histamine therapy may not be due to the supposedly increased tolerance developed to histamine, but may be due to the pharmacological action of the drug, such as its action on the capillaries,[1] special vascular beds,[5] or the increased oxygen uptake.[8]

Many of these compounds are not destroyed by histaminase and, therefore, may lend themselves to oral administration.

Whether or not any of the compounds which are reported are satisfactory cannot be stated at this writing. However, it is possible that there are other compounds which would be the perfect answer to the problem.

SUMMARY

Eighteen derivatives of histamine have been synthetized and described as to their histamine-like action, the liberation of histamine, or prolonged histamine-like reaction. The clinical results for several of these compounds are given. It is pointed out that the therapeutic results of histamine therapy may be due to its pharmacological action and not to increased histamine tolerance. The compounds may be effective orally.

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PATTERNS OF ALLERGIC SENSITIZATION

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THERE are probably well over 100 species of plants whose pollen contributes in some way to the production of hay fever and should be accounted for in attempting to control a patient's symptoms. It is manifestly impracticable for the manufacturer or the medical practitioner to maintain stocks of all, or for the latter to use so many in the diagnosis and treatment of his cases. This difficulty is generally circumvented in one of two ways, either by making up various combinations of pollens to suit the patient and the time and the place of his hay fever, or by letting one species of pollen represent a more or less restricted group of taxonomically related species. Yet it has been far from adequately demonstrated to what extent the serological relations of the various hay-fever pollens correspond to the taxonomy of the plants. Consequently it is questionable to what extent the first procedure is necessary or the second justifiable. Much useful information regarding the serological relationships of allergens has been obtained from their cross neutralizations of local passive transfer sensitizations by the Prausnitz-Küstner technique. However, recent studies by several different investigators have shown that the phenomenon is much more complicated than formerly supposed. Sera are not alike in their sensitizations; each has its own and highly exclusive reaction pattern. These patterns must be understood in order to interpret the test properly.

The test is made as follows. Sites are sensitized by the injection of 0.1 c.c. or less of the serum of an allergic patient into the superficial layers of the skin of a normal recipient. After a day or two these are reinjected with a minute amount of the allergenic material to be tested. The sensitized site reacts to its homologous allergen in about the same way that the skin of the donor of the serum reacted to the same substance. If the allergen was used in a low concentration, a second or even third reaction may be elicited at the same site, but eventually it becomes exhausted or desensitized for that particular allergen. However, it may remain active to others to which the donor was sensitive.

By means of this technique, it was long ago found that if the serum of a timothy-ragweed hay-fever case is used to sensitize the sites, when desensitized to ragweed they may remain active to timothy. Or if desensitized to timothy they may remain active to ragweed. This was interpreted to mean that the timothy and ragweed antigens were qualitatively different and that there is a specific antibody (reagin) corresponding to each specific antigen. On the other hand, if the tests with the first allergen neutralized the site to a substance of another source, and to which it would otherwise

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have responded, the two were pronounced antigenically the same. Thus a site sensitized with the serum of a ragweed hay-fever patient was found to react freely with either the short or tall ragweeds, and if desensitized by one it likewise became insensitive to the other. This was interpreted to mean that the two ragweeds were antigenically identical. And since the tall and short ragweeds are biologically closely related, and ragweed and timothy are not, this cross neutralization was thought to be correlated wih the taxonomic relationships of the pollen species. Among those less closely related, less agreement was encountered in cross neutralizations. Thus, when sites were sensitized with the serum of a grass hay-fever patient, it was found that timothy would neutralize its sites against June grass and orchard grass, and that June grass would neutralize them against timothy, but orchard grass failed to neutralize its sites against timothy. This was interpreted to mean that timothy represented the antigenic properties of all the grass family but that orchard grass was deficient in some. From these and a few similar experiments it was generalized, and almost universally accepted, that with the method of desensitization of passively sensitized skin sites, the identity or nonidentity of atopens of different origin can be determined. And those that were closely related in origin had the same or similar antigenic complex.

Perhaps the first to cast doubt upon this comfortable theory was Clarke (1927) who showed that a strong reaction of one allergen in a passive transfer site might render the site inactive on subsequent tests with unrelated allergens, the neutralization depending upon the relative strengths of the reagins of the serum. At a later date (1937) he said that when the reagin was present in a weak concentration it was subject to neutralization by almost anything, but when present in sufficient concentration so that two or more skin tests were necessary to neutralize it, no matter what was done the stronger reaction persisted.

With Sherman and Stull (1938), this concept of major and minor sensitizations emerged as their theory of dominance. They found that cross reactions depend much more upon the patient than upon the relationships between the allergens. Thus when the sera of three patients who were sensitive to dogs and cats were compared, sites sensitized with the first serum and neutralized by dog dander were found to be also insensitive to cat dander, but cat dander failed to neutralize them against dog. With the second serum the cat dander would neutralize the sites against dog, but not the reverse. And with the third serum cat and dog antigens were mutually neutralizing.

Similarly, among pollens they found that with the serum of a late hay-fever case, also sensitive to timothy, ragweed would neutralize the sites against timothy, but not the reverse. And with the serum of a grass hay-fever case, timothy would neutralize its sites against hickory, plantain, oak and sorrel, but none of these affected at all the timothy sensitization. Occasionally even one-way neutralizations were found against entirely

unrelated atopens as between horse dander and ragweed. They concluded that, "In the case of serums which reacted strongly to one antigen and less actively to several others, the most active antigen usually neutralized the serum to test with all the antigens." And, "It is apparent that the cross neutralization reactions obtained depended upon the serum tested and did not represent a constant relationship between the antigens." This they partly explain by saying that, "the reaction is analogous to the absorption of antibody by bacterial antigens." Indeed, the present report will show that the cross neutralizations among pollen species almost exactly parallels the agglutinin absorptions by the salmonella and typhoid bacteria, for example. These authors furnish a comprehensive review of the literature previous to 1938. Hence, only work subsequent to that date need be mentioned.

An interesting parallel is found among patients who are allergic to fish. Tuft and Blumstein (1946) have found that those who are sensitive to fish among the Teleostii, the group which includes practically all edible fishes, would react by skin test to fish with which they had never been in contact, even those of the Elasmobranchii, the group of inedible sharks and rays. But by cross neutralization tests it was found that the atopen of a teleost fish could neutralize the transfer sites to all fish, even to the inedible elasmobranchs, but never could the latter neutralize the sites to the edible teleosts.

Prince and Secrest (1939) showed that with the sera of some patients with hay fever in Houston, marsh elder would neutralize its sites against short, tall and western ragweed, but none of these would neutralize their sites against marsh elder. In Houston the three ragweeds (Ambrosia) and the related marsh elder (Iva) are regarded as important causes of hay fever. Obviously in some cases, Iva may be the major sensitization, and its antigenic structure is not identical with that of the ambrosiae.

Cooke (1944) says, "It is a common thing to find patients giving multiple reactions. Are these due to one or to many different antibodies each reacting with its own antigen?" He answers the question by showing the reactions of the serum of a patient sensitive to twenty-two different antigens, including pollens of all the taxonomic categories, orris root, Alternaria and Lycopodium spores, cotton, kapok and flax seeds. This serum was mixed with ragweed extract in sufficient concentration to neutralize it to test with ragweed, and used to prepare twenty-two sites in the skin of a normal individual. Subsequent tests showed that the ragweed had neutralized the reagin for all the allergens except plantain and sorrel.

The patient was treated with ragweed alone. It was found by a serum dilution test after treatment that the ragweed reagin was increased, as usually happens, in this case fourfold. And significantly, the reagin for plantain was also increased approximately fourfold. The author states, "This one of many such observations makes it seem probable that there is but one basic antibody unit so to speak, but with at least two prosthetic

TABLE I. IN VIVO DESENSITIZATION, PAR. SERUM, 1:25
Reactions at Sensitized Sites

1st Test, 1000 units p. c.c.			2nd Test, 2000 u. p. c.c.		Reciprocal Test, 1000 u. p. c.c.		
Antigens	w	e	w	e	Antigen	w	e
Common mugwort	9	35	6	10	Sagebrush	5	0
Silvery wormwood	10	40	6	0	Sagebrush	6	0
Calif. mugwort	8	30	5	0	Sagebrush	5	0
Green sage	11	30	6	0	Sagebrush	8	0
Coast sagebrush	13	40	7	10	Sagebrush	6	0
Pasture sage	11	25	5	0	Sagebrush	5	0

Table I. Reactions obtained at sites in the skin of a normal recipient sensitized by the intracutaneous injection of 0.05 c.c. of Par. serum, diluted 1:25, tested 4 hours later with 0.01 c.c. of each of the pollens shown in the left hand column, 1,000 nitrogen units per c.c. w = average diameter of the wheal and e = the over-all diameter of the erythema.

groups, one reacting with ragweeds and those antigens it neutralized, and another reacting with plantain." From this and the reactions of other sera it appears that, "The antibody in any particular serum when studied in detail with regard to reactions and neutralizations has what approaches a fingerprint individuality."

It would have been interesting to know if the patient with twenty-two sensitizations benefited from treatment with ragweed alone and if the benefit extended to his other sensitizations of both prosthetic groups, or if the untreated sensitizations were made worse owing to the fourfold increase of their reagins. The author points out that the blocking antibody engendered by treatment, in contrast to the sensitizing antibody, is highly specific. So much so that a patient treated with ragweed and developing a blocking antibody for ragweed, developed none for cocklebur nor for sagebrush, even though his transfer sites were neutralized for both by ragweed. If the blocking antibody is the protective mechanism, it follows that treatment with a single pollen species could only protect against the pollen of that particular species and might even aggravate the patients' sensitizations to the others.

The present study was designed to discover the antigenic structure of pollen allergens, and the correlations between their taxonomy and the patterns of their sensitization. The patterns of immunization are the subject of a study now in progress.

Case 1.—Par. was a resident of Los Angeles, where it appears she developed her hay fever. By direct intracutaneous tests she proved to be sensitive to most of the grasses, the ragweeds and their relatives, the Chenopods and Amaranths, the sagebrushes and mugworts. She was regarded by her physician as a case primarily of sagebrush and grass hay fever, and was being treated with a mixture of twelve different extracts representing all the main groups of pollen.

Her serum was used to sensitize six sites on a normal recipient. A serum dilution experiment had shown that this serum could be used diluted to 1:25 and still give good sensitizations. So this was the dilution chosen.

After twenty-four hours the sites were tested with extracts of the pollens of six members of the genus Artemisia (Table I). The reactions were recorded as the average diameters of the wheals and the over-all diameters of the erythemas. It

TABLE II. IN VITRO NEUTRALIZATION, PAR. SERUM, 1:25
Reactions at Normal Sites and their Retests

Immediate Reactions			2nd Test, 2000 u. p. c.c.		Reciprocal Test, 1000 u. p. c.c.		
Antigens	w	e	w	e	Antigens	w	e
Sagebrush	12	15	6	0	Common mugwort	6	0
Sagebrush	10	12	6	0	Silvery wormwood	6	0
Sagebrush	11	20	8	0	Calif. mugwort	7	0
Sagebrush	11	22	8	0	Green sage	7	0
Sagebrush	11	15	10	0	Coast sagebrush	5	0
Sagebrush	11	17	8	0	Pasture sage	6	0

Table II. Reactions obtained at unsensitized sites in the skin of a normal recipient, when injected intracutaneously with 0.05 c.c. of mixtures in equal parts of Par. serum, 1.25 + pollen extracts, 1,000 units per c.c. followed by 0.01 c.c. of the same pollen at 2,000 units per c.c., and their reciprocal tests with pollen extracts at 1,000 units per c.c. For explanation see Table I.

will be seen that all of the artemisiae gave reactions, though some more than others. The next day the sites were reinjected with the same antigens at double the concentration. Only two of them, common mugwort and coast sagebrush, gave even borderline reactions on the second tests, showing that the first reactions had nearly or completely desensitized the sites for the allergens used. Any residual sensitizations could certainly be counted upon to be sufficiently neutralized by the second test. The sites were then all tested with sagebrush extract, also a number of the genus Artemisia. Every site was found to be completely negative to sagebrush.

This is the method of *in vivo* desensitization. Since the sites are sensitized first, then tested, it has the advantage of discovering which antigens will elicit reactions, and gives a rough idea of the degrees of the specific activities of the serum. When these are known, the experiment can as well be done by combining the antigen with the serum and preparing sites by injecting the combination. This is known as *in vitro* neutralization. It has the advantage of requiring one less injection and gives essentially the same results, but the immediate reactions are unrealiable, so the use of the method is restricted to allergens to which the reactions of the serum under consideration are already known.

Returning to the Par. serum, the reverse of the preceding experiment was tried. Since it was already known that sagebrush elicited reactions with this serum comparable with the most active of the other members of the genus, the *in vitro* method was used. Sagebrush extract was combined with the serum in a proportion which it was believed would completely neutralize it, and six sites were prepared by injecting the combination. Twenty-four hours later the sites were reinjected with double the concentration of sagebrush (Table II). No reactions were obtained, showing that neutralization had been complete. The sites were next tested with each of the six other members of the group. None caused reactions, showing that with this serum sagebrush is capable of neutralizing its sensitivity to at least these six other members of its genus. And since the reverse is also true, it is reciprocally neutralizing with them as if antigenically identical.

When other sensitizations of this serum were tested in the same way (Fig. 1) it was found that bur ragweed and western ragweed only partially neutralized their sites against sagebrush. Tall, short and slender ragweeds had no appreciable effect on their sites against sagebrush. But sagebrush neutralized its sites to all of these. When these latter extracts were tested against each other they proved to be recipro-

cally neutralizing. Even bur ragweed and western ragweed, both of which could partially neutralize the sagebrush sensitization, were reciprocal with short and slender ragweed, which had no neutralizing effect on it.

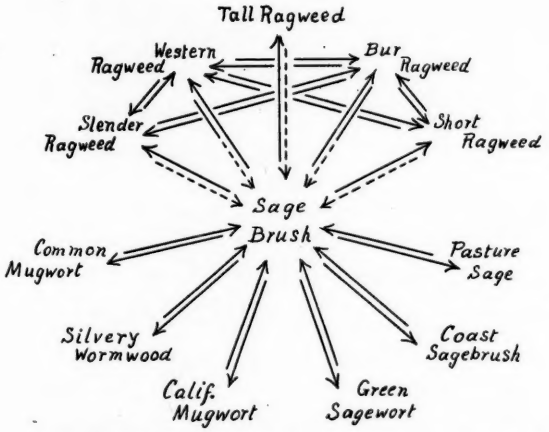

Fig. 1. Diagram of cross reactions, Par. serum. The direction of the arrowheads indicates the sequence of the tests. The unbroken line indicates that the first test neutralized against the second completely; the broken line indicates no appreciable reduction in the second test; and the partly solid and partly broken line indicates that the first test materially reduced the reaction of the second but was never able to completely obliterate it.

In this serum, sagebrush is in the major position but it is reciprocal with all the other members of its genus (lower half of the diagram). It neutralizes its sites to all other sensitizations (upper half of the diagram) but none of these is able to neutralize its site against sagebrush. Only bur ragweed and western ragweed can partly do it, and these, in turn, are reciprocal with each other and with slender and short ragweeds.

This shows that the major antigen of sagebrush is identical with those of the other species of Artemisia, and that sagebrush contains an antigen common to the ragweeds which is not their major antigen.

Russian thistle, summer cypress and perennial ryegrass gave only borderline reactions, and cat dander, timothy, June grass, Bermuda grass and California black walnut, to all of which the patient reacted by direct test, failed to transfer with the serum concentration used.

This is a simple form of multiple sensitization. The patient's major sensitization is to the major antigen of sagebrush, and this is shared by all the species of Artemisia. Sagebrush also contains a minor antigen which is common to the members of the ragweed group.

Case 2.—Gip. was a Santa Fé stationery engineer at Prescott, Arizona, a region characterized by cedars, sagebrush, Russian thistle and western ragweed. He gave a history of severe hay fever since 1931, starting as early as January or February and lasting at first until May, virtually coinciding in extent of time with the pollination of the several species of juniper and cypress in northern Arizona. However, year by year, his symptoms became worse and lasted longer, eventually developing into asthma and reaching the end of summer. Clearly he was becoming clinically more sensitive and affected by more pollens.

At the time when his serum was obtained (1944), his case was recognized as

TABLE III. IN VIVO NEUTRALIZATION, GIP. SERUM
Reactions at Sensitized Sites

1st Test, 1000 units per c.c.			2nd Test, 2000 u. p. c.c.		Reciprocals, 1000 units p. c.c.		
Antigens	w	e	w	e	Antigens	w	e
Carelessweed	8	35	6	0	Mountain cedar	10	40
Summer cypress	8	35	6	0	Mountain cedar	10	40
Bermuda grass	6	20	6	0	Mountain cedar	8	45
Timothy	5	0					
Sagebrush	9	25	5	0	Mountain cedar	8	30
Mountain cedar	9	40	6	12	Carelessweed	6	0
Mountain cedar	10	45	5	0	Summer cypress	7	0
Mountain cedar	11	40	7	0	Bermuda grass	5	0
Mountain cedar	11	40	7	0	Sagebrush	6	0

Table III. For explanation see Tables I and II.

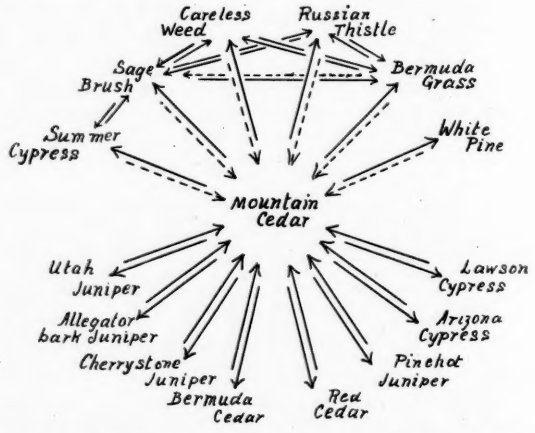

Fig. 2. Diagram of cross reactions of Gip. serum. For explanation of signs see Figure 1. Mountain cedar is in the major position but reciprocal with all members of its own genus, Juniperus, and the related Chamaecyparis (lower half of diagram).
This shows that mountain cedar has a major antigen common to its group and minor antigens common to six unrelated pollens.

primarily due to the cedar pollens. By direct test he gave unusual reactions rated at 4+ to the pollen of the four species of cedar with which he was tested. He also reacted strongly to Bermuda grass, sagebrush, Russian thistle, carelessweed, summer cypress, and other later-flowering plants. He was being treated with a combination of extracts, including the principal representatives of all the taxonomic groups, and had secured considerable clinical improvement.

His serum was used to sensitize sites on normal recipients. These were tested with seven species of juniper and two of cypress. By cross neutralization tests all were found to be reciprocally neutralizing with mountain cedar, just as the members of Artemisia were reciprocally neutralizing with sagebrush in the serum of Case 1.

But besides this the sensitized sites reacted less strongly to carelessweed, summer cypress, Bermuda grass and sagebrush. After they were desensitized by these, they remained fully active to moutain cedar. On the other hand, if they were first desensitized by mountain cedar, they proved to be insensitive to carelessweed, summer cypress, Bermuda grass and sagebrush. Cross neutralization tests with these showed that they were not all completely reciprocal (Fig. 2), as were the

members of the ragweed group with Par. serum. In this case Bermuda grass failed to neutralize the sites against sagebrush.

Clearly the major sensitization of Gip. serum is to the major antigen of mountain cedar, and this is identical with that of the other junipers and

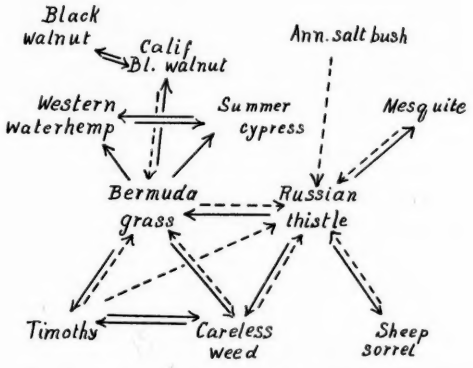

Fig. 3. Diagram of cross reactions of Ra. serum. For explanation of signs see Figure 1. Russian thistle is the major sensitization and is not reciprocal with anything.

cypress. Taxonomically these represent two genera (Juniperus and Chamaecyparis) of the Cupressineae, which is one of the six tribes of the Coniferae. Mountain cedar also has minor antigens which are common to summer cypress, carelessweed, Russian thistle, Bermuda grass, and these are not their major antigens nor are they all the same.

The Gip. serum was also tested with the pollens of related conifers, white pine, Douglas fir and hemlock of the tribe Abietineae, redwood of the Taxodineae, and yew of the Taxineae. It reacted only to the pollen of pine. However, neutralization by pine left the sensitization unimpaired to mountain cedar, while neutralization by cedar completely neutralized the pine sensation putting it in the same category as sagebrush, Russian thistle or Bermuda grass (Fig. 2). Thus it is seen that the specific antigen of the Cupressineae which corresponds to Gip.'s major sensitization, is not found in less closely related members of the Coniferae, as far as these were tested.

Since this patient's hay fever extended throughout most of the summer season, long past the pollinating period of the junipers and cypress, he owed the greater part of his clinical symptoms to minor antigens which are common to mountain cedar and unrelated species.

Case 3.—Ra., a resident of Los Angeles, had hay fever most of the summer. By direct test he reacted to almost every allergen tried, including sixteen species of grass, the ragweeds, amaranths and chenopods. It was concluded from his history and tests that his hay fever was primarily due to grasses. When his serum was obtained, he was being treated with extracts of seven species of grass and a heterogeneous mixture of other things in an attempt to cover all his sensitizations.

Since Bermuda grass was the most important plant flowering during the time when the patient had his worst symptoms, it seemed most likely to be the major cause of his allergy. It was put to the test (Fig. 3). This pollen neutralized some of his most important sensitizations, summer cypress, western waterhemp, California black walnut, timothy and carelessweed, but it failed to neutralize his Russian thistle sensitization. Russian thistle, however, neutralized his Bermuda sensitization. Hence, with this serum Russian thistle sensitization is predominant over that of Bermuda grass. Russian thistle was then tested against the remaining important sensitizations, sheep sorrel, mesquite and annual saltbush, and found to predominate over them. Hence, Russian thistle is Ra.'s over-all major sensitization. This pollen is not reciprocal with carelessweed nor any of the other members of the Chenopod-Amaranth group with which it was tested.

This case is of particular interest because a large proportion of the patient's clinical symptoms came from the minor antigen or antigens common to Russian thistle and the other pollens, so much so that he was regarded as primarily a grass case. This was probably due to the fact that his exposure to the minor grasses was greater than to his major Russian thistle.

Case 4.—Boi. was an engineer whose work required him to travel extensively. He had lived in England and several European countries and in both the eastern and western parts of the United States, and wherever he went he had hay fever, in the United States both early and late. His serum was taken in Los Angeles in November, and he was experiencing mild symptoms then. He reacted by direct test to practically every pollen which was tried; also to animal epidermals, mold, egg and some other foods. He was recognized as a Class A grass case and a most extreme example of multiple sensitization.

When his serum was taken, he was being treated with sixteen different pollens, ten grasses, two artemisias, one ragweed, and three chenopods, as a defense against the hay fever flora of California. He expected to be sent to Northern Ireland on war work so his doctor had prepared another combination better representing the hay fever flora of that country, to take with him.

When this serum was tested by passive transfer it was found to react to twenty-one different pollens, all but three that were tested. Red cedar, Arizona cypress and Lawson cypress were negative to test, though by direct intracutaneous test the patient had given a moderate reaction to mountain cedar of this group. It did transfer. Also horse and cat dander, and egg white sensitizations failed to transfer, though by direct test the patient had reacted to them.

Neutralization tests showed that timothy neuralized its sites completely to all other pollens which were tested. And only orchard grass, perennial ryegrass and sweet vernalgrass would neutralize their sites against timothy (Table IV).* All others, including Bermuda grass, June grass and redtop, left their sites fully reactive to timothy.

The major sensitization of Boi. serum, therefore, is to the major antigen of timothy. And since orchard grass, perennial ryegrass and sweet vernalgrass are reciprocal with it and with each other, the major antigen of timothy is also the major antigen of these. Moreover, these four grasses also

*The material upon which this report is based is recorded in more than sixty protocols of which Table I-III are typical examples. It is felt that the reference value that these might have does not warrant their inclusion here. However, they are a part of our laboratory record where they will be available for references as long as the possibility of their need shall appear to exist.

TABLE IV. BOI. SERUM
Retest Reactions

Antigens Used in Neutralization or Desensitization	Timothy	Bermuda grass	June grass	Orchard grass	Perennial ryegrass	Sweet vernalgrass	Redtop	Careleasweed	Russian thistle	Sheep sorrel	Black walnut	Oak	Olive	Sycamore	Poplar	Mountain cedar	Utah juniper	Allegator bk. juniper	Cherrystone juniper	Ragweed	Sagebrush
Timothy		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				0	
Bermuda grass	+		+	+	+	+	+	0	0		0	0	0			0					0
June grass	+	0		0		0	0				0					0					
Orchard grass	0	0	0		0	0	0		0		0	0				0					
Perennial ryegrass	0	0		0		0	0		0		0										
Sweet vernal grass	0	0	0	0	0		0		0		0										
Redtop	+	0	0	0	0	0			0		0	0				0					
Carelessweed	+	0							0		0					0					
Russian thistle	+	0		+	+	+	+	0			0	0				0					
Sheep sorrel	+																				
Black walnut	+	0	+	+	+	+	+	0	0												
Oak	+	±		+			+		0												
Olive	+	+																			
Sycamore	+																				
Poplar	+																				
Mountain cedar	+	+	+	+			+	0	0								0	0	0	0	0
Utah juniper																0					
Allegator bk. juniper																0					
Cherrystone juniper																0					
Short ragweed	+															0					0
Sagebrush																0				0	

Table IV. The retest reactions of sites sensitized by Boi. serum. The sites were desensitized by, or the serum used to prepare them was "neutralized" by, the pollen extracts in the left hand column, neutralization proved, then tested with those in the top horizontal column. The reactions obtained are recorded in vertical columns beneath the names of the retest extracts. "0" indicates that no reaction was obtained with the retest. "+" indicates that the reactivity of the site was not significantly impaired to the test by the first reaction. "±" indicates that the retest reaction was always significantly reduced, but never completely neutralized by the first test reaction.

A convenient way to read the table is by horizontal and vertical lines. Reading the first horizontal line tells that timothy neutralized its sites to everything against which it was tested. The second tells that Bermuda grass failed to neutralize its sites to any grass but did so to all other pollens outside of the grass family. Reading the first vertical column tells that only orchard grass, perennial rye grass and sweet vernal grass neutralized their sites against timothy. And since timothy also neutralized its sites against these three grasses they are reciprocal with timothy. Reading the second vertical column tells that all except oak, olive and mountain cedar neutralized their sites against Bermuda grass. And Bermuda grass is reciprocal with careless weed, Russian thistle and black walnut, but not with any grasses.

behave exactly alike in their cross reactions with other species as far as these have been tested with this serum, though slight differences are brought to light in their reactions with other sera, for example Rod. serum (Table VI), in which mountain cedar neutralizes to sweet vernalgrass but not to orchard and only partly to timothy and perennial ryegrass. Hence, these four grasses are very nearly identical in both their major and minor antigens. On the other hand, Bermuda grass, and even June grass and redtop, are antigenically different from timothy, though the latter two are less so than Bermuda grass.

The position of Bermuda grass reagin in this serum is minor to that of timothy and all the other grasses with which it was tested. While the other grasses neutralized their sites to everything to which they were tested, ex-

cept to timothy, Bermuda grass failed to neutralize its sites to any other grass. And all other grasses, including the minor redtop and June grass, neutralized their sites to Bermuda grass. Even the totally unrelated Rus-

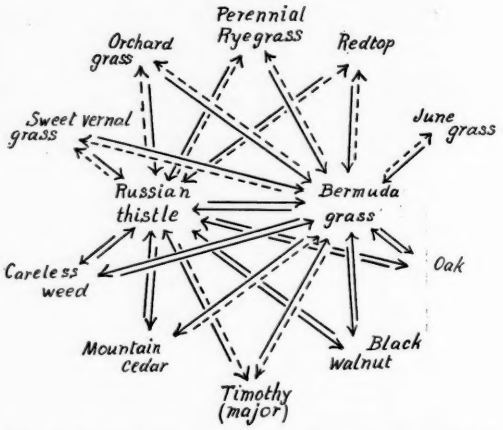

Fig. 4. Diagram showing comparison of unrelated reciprocals in the minor position with Boi. serum. They behave alike in all their relations except with mountain cedar which neutralizes Russian thistle sensitization but fails to neutralize that of Bermuda grass. For explanation of signs see Figure 1.

sian thistle carelessweeds, and black walnut do also. In other words, Bermuda grass entirely lacks the major grass antigen. On the other hand, this is probably shared by June grass and redtop which appear to lack only a specific timothy antigen since they differ only in failing to neutralize their sites to it.

Bermuda grass in this case is reciprocal with Russian thistle though entirely unrelated to it (Fig. 4). Both are reciprocal with oak and black walnut which are unrelated to either, and with carelessweed which is related to Russian thistle. They are both minor to all four grasses with which they were tested. In fact the only difference between the behavior of Bermuda grass and Russian thistle is with mountain cedar. With this pollen Russian thistle is reciprocal but the Bermuda grass sensitization is not neutralized by it. Bermuda grass behaves more like Russian thistle to which it is unrelated than it does like timothy to which it is taxonomically closely related. These reactions must, therefore, be due to the minor antigens. Bermuda grass has an antigen which is common to Russian thistle, carelessweed, black walnut and oak. It is not a major antigen because as we shall see with Rod. serum, containing the Bermuda major reagin, the Bermuda antigen neutralizes against everything but is reciprocal with nothing. The six other grasses have an antigen not in Bermuda and which is certainly the major antigen of all except possibly redtop and June grass, since the others are reciprocal with the major timothy. Russian thistle like Ber-

muda grass, lacks the major grass antigen but has a minor antigen common to the five grasses.

With Boi. serum, Bermuda grass and black walnut are reciprocal and

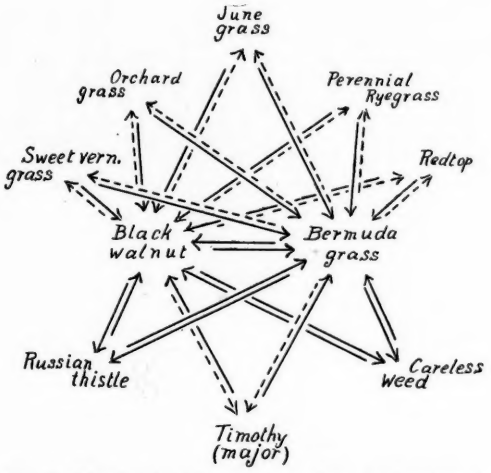

Fig. 5. Diagram showing comparison of unrelated reciprocals, Boi. serum. They behave alike in all respects. For explanation of signs see Figure 1.

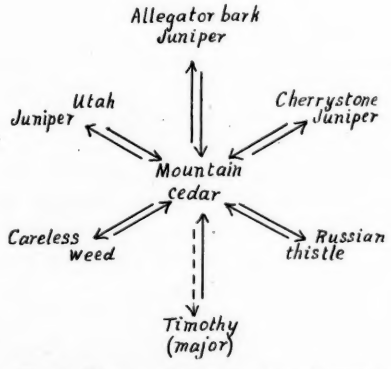

Fig. 6. Diagram of cross reactions of mountain cedar when in the minor position, Boi. serum. Mountain cedar is reciprocal with three members of its own genus, also with Russian thistle and carelessweed. Compare with Figure 2.

behave alike in all respects as far as tested. Both are reciprocal with Russian thistle and carelessweed to which they are totally unrelated, and both are minor to all the grasses (Fig. 5). Thus these two pollens also possess the same minor antigen or antigens.

The difference between the behavior of atopens towards reagins, whether

TABLE V. JAM. SERUM
Retest reactions following neutralization

Antigens Used in Neutralization Tests	Timothy	Bermuda grass	Johnson grass	June grass	Orchard grass	Perennial ryegrass	Sweet vernalgrass	Redtop	Carelessweed	Oak	Poplar	Birch	Pecan	Elm	Willow	Short ragweed	Tall ragweed	Western ragweed	Slender ragweed	Burweed marshelder	Marshelder
Timothy		0	0	0	0	0	0	0	0	0	0		0	0	0	0	0				0
Bermuda grass	+				+																
Johnson grass	+				+																
June grass	+				+																
Orchard grass	0	±	0	0		0	0	0													
Perennial ryegrass	0				0																
Sweet vernalgrass	0				0																
Redtop	0				0																
Carelessweed	+																				
Oak	+																				
Poplar	+																				
Birch	+																				
Pecan	+																				
Elm	+																				
Willow	+																				
Short ragweed	+																0	0	0	0	
Tall ragweed	+															0					
Western ragweed																0					
Slender ragweed																0					
Burweed marshelder																0					
Marshelder	+																				

Table V. The retest reactions of Jam. serum. For explanations see Table IV. The relations between timothy and Bermuda grass are similar but not identical with those in Boi. serum.

in the major or minor position, is strikingly brought out by comparing the reactions of the Cupressineae with the Gip. serum in which they were major, with those of the Boi. serum in which they are minor. With the Gip. serum, mountain cedar was reciprocal with them all but major to everything else. With the Boi. serum (Fig. 6), Red cedar, Arizona cypress and Lawson cypress sensitizations fail to transfer. Mountain cedar is found to be reciprocal with Utah juniper, alligator bark juniper and cherry-stone juniper, but more significantly, it is also reciprocal with careless-weed and Russian thistle, to both of which it is unrelated. This shows that the reciprocal neutralizations that do occur within the Cupressineae are here due to minor antigens which occur also in unrelated species.

Case 5.—Jam. was a resident of Shreveport, Louisiana, where it is believed she contracted hay fever in 1932. When her serum was taken in 1947, she was having severe hay fever from mid-February to mid-June. By direct test she had been found sensitive to all pollens tested, to dust, feathers, cat, dog and horse danders. Immunization had been attempted but never carried out on account of frequent and severe constitutional reactions.

Her serum was found to react to twenty-one different pollens (all that were tested), but the dust and epidermal sensitizations failed to transfer at the concentrations required for the pollens. Timothy was found to be the major sensitization (Table V), and as in the case of the Boi. serum it was reciprocal with orchard

TABLE VI. ROD. SERUM
Retest reactions following neutralization

Antigens Used in Neutralization Tests	Bermuda grass	June grass	Perennial ryegrass	Redtop	Timothy	Orchard grass	Sweet vernalgrass	Carelessweed	Russian thistle	Summer cypress	Shadscale	Western waterhemp	Sagebrush	Short ragweed	Western ragweed	Oak	Poplar	Black walnut	Calif. black walnut	Mesquite	Mountain cedar	Sheep sorrel
Bermuda grass	.	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0		0	0	0	0
June grass	+			0	0																	
Perennial ryegrass	+			0	±			0				0									0	
Redtop	+	0	0		0	0	0	±				0									0	
Timothy	+	0	0	0		0	0	0	0	0		0			0						0	
Orchard grass	+			0	0			0													0	
Sweet vernal grass	+			0	0			0													0	
Carelessweed	+		0	0	0	0	0		0	0		+										
Russian thistle	+				+			0		0		0										
Summer cypress	+				+			0	0			0										
Shadscale	+																					
Western waterhemp	+		±		+			0	0	0											0	
Sagebrush	+																					
Short ragweed	+														0							
Western ragweed					0									0								
Oak	+																					
Poplar	+																					
Black walnut																			0			
Calif. black walnut	+																	0				
Mesquite	+																					
Mountain cedar	+		±	0	0	+	0					0										
Sheep sorrel	+																					

Table VI. The retest reactions of Rod. serum. The relations of timothy and Bermuda grass are the reverse of those of Boi. and Jam. sera. Bermuda grass is the sole major sensitization. Timothy is reciprocal with June grass, orchard grass, redtop, and sweet vernal grass, but not with perennial rye grass among the grasses. On the other hand, it is reciprocal with carelessweed and western ragweed outside of the grass family.

grass, perennial ryegrass and sweet vernalgrass. But unlike the previous serum, timothy is here also reciprocal with redtop. It neutralizes against Bermuda, Johnson and June grasses but is not neutralized to test by them, except partly by June grass. Orchard grass behaves the same as timothy in relation to the other grasses except that it only partially neutralizes the Bermuda sensitization, showing that the reciprocals among the majors are almost but not quite identical.

In this serum the ragweeds are subordinate, and it is seen that tall, western and slender ragweeds and burweed marshelder are reciprocal with short ragweed. This should be compared with the pattern of the Spri. serum *(vid. ult.)* in which short ragweed is major. In the major position it is not reciprocal with slender ragweed and burweed marshelder. They do not interreact in the major position; hence, their interreaction in the minor position is through a common minor antigen.

Case 6.—Rod. was a resident of Los Angles suffering from both early and late hay fever. By direct test she reacted to practically every pollen with which she was tested, representing all taxonomic groups, and to the animal epidermals, egg and glue. She was recognized as a case of extreme multiple sensitization and was being

treated with seven grasses and a combination of chenopods, amaranths, ragweeds and artemisias in an effort to cover as many of her sensitizations as possible.

By passive transfer her serum sensitized to twenty-two different pollens—all that were tested (Table VI). Cross neutralization tests showed that Bermuda grass

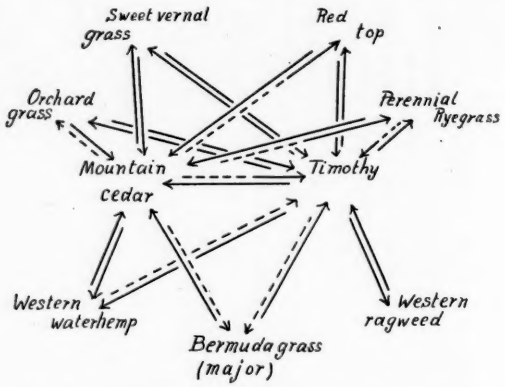

Fig. 7. Diagram showing comparison of cross reactions of unrelated half reciprocals in the minor position, Rod. serum.

neutralized its sites against all other pollens and none of them neutralized their sites against Bermuda grass. It is the sole major sensitization, finding no reciprocals among the pollens tested. The relative positions of timothy and Bermuda grass sensitizations are the reverse of what they were with the two preceding sera, and as a result timothy behaves quite differently. With this serum, timothy neutralizes its sites against all except Bermuda grass. It is reciprocal with June grass, orchard grass, redtop and sweet vernalgrass, but not with the equally related perennial ryegrass. On the other hand, it is reciprocal with the entirely unrelated carelessweed and western ragweed, showing that timothy possesses minor antigens which are common to these, though unrelated.

The wide minor-antigenic coverage of the Rod. serum reagins provided opportunity to examine the specific relations of the minor antigens. Our analysis is based on the results diagrammatically presented in Figures 7 to 9. First it is seen that the major antigen of Bermuda is lacking in carelessweed, timothy, Russian thistle and western waterhemp, because none of these desensitized to Bermuda (Table VI). Equally important is the conclusion that none of the major antigens of these four pollens is represented in the Rod. sensitization because Bermuda does desensitize to all of them. Hence, in the reciprocal tests with those four pollens, we were dealing only with minor sensitivities. This conclusion is also supported by the complete reciprocity between timothy pollen and western ragweed (Fig. 8), which again proves the absence from Rod. serum of reagins for the major antigens of these two pollens.

The mutual complete reciprocity of desensitizing property among timothy, carelessweed, orchard grass and sweet vernalgrass speaks for identity of

the minor antigens of those pollens with respect to Rod. serum. However, the further analysis is confronted by the apparent contradictions in the other reciprocal tests. Thus, carelessweed reciprocates wholly with timothy and with summer cypress; yet summer cypress seems to lack some minor

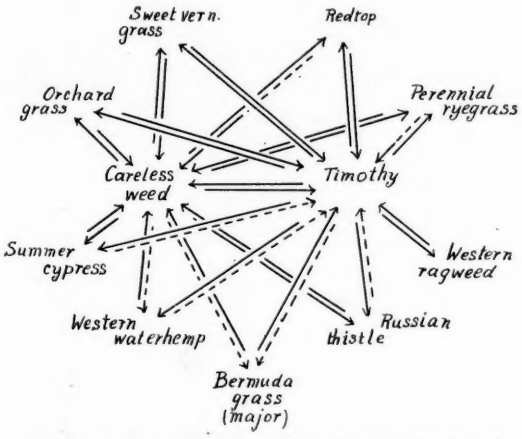

Fig. 8. Diagram showing comparison of unrelated reciprocals, in the minor position, Rod. serum. Careless weed and timothy are alike in their relations with orchard grass, sweet vernalgrass and the major Bermuda grass but differ in their other relations.

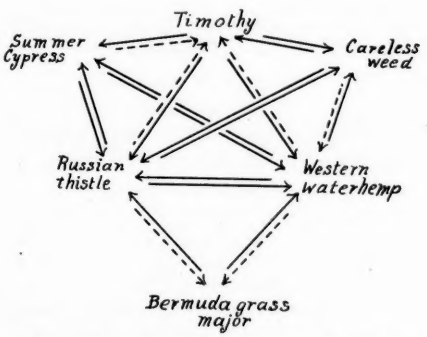

Fig. 9. Diagram showing comparison of cross reactions between related reciprocals in the subordinate position, Rod. serum.

antigen which is present in timothy. In other words, although both timothy and summer cypress equal carelessweed, they do not equal each other. This contradiction seems inexplicable purely in the terms of partial antigens; and it needs further study since other similar instances of it are seen in these studies. Thus carelessweed and western waterhemp are equal to Russian thistle but not to each other (Fig. 9); also Russian thistle and timothy are equal to carelessweed but not to each other.

TABLE VII. SPRI. SERUM
Retest reactions following neutralization

Antigens Used in Neutralization Tests	Western ragweed	Short ragweed	Tall ragweed	Slender ragweed	Bur ragweed	Cocklebur	Burweed marshelder	Marshelder	Sagebrush	Plantain	Western waterhemp	Carelessweed	Russian thistle	Summer cypress	Lambsquarters	Bermuda grass	Timothy	Pecan	Ash	Oak	Birch	Elm	Mountain cedar
Western ragweed		0	0	0	0	0	0	0	0	0	0	0	0			0	0						0
Short ragweed	0		0	0	0	0	0	0	0														0
Tall ragweed	±	0		0	0	0	0	0	0														0
Slender ragweed	±	0	0		±	0	±		0														0
Bur ragweed	0	0	0	0		0	0		0														0
Cocklebur	+	±	±	0	+		0	±	0	0													0
Burweed marshelder	+	±	±	±	±	0		0	0	0													0
Marshelder	+	+	+			0	0		0	0													0
Sagebrush	±	±	±	0	+	0	0	0		0													0
Plantain	+					0	+	+	+		0						0						0
Western waterhemp	+									0													+
Carelessweed	+																						
Russian thistle	+																						
Summer cypress	+																						
Lambsquarters	+																						
Bermuda grass	+																						
Timothy	+									0													
Pecan	+																						
Ash	+																						
Oak	+																						
Birch	+																						
Elm	+																						
Mountain cedar	+	+	+	+	+	0	+	+	0	0	0												

Table VII. The retest reactions of Spri. serum. Western, short and bur ragweeds are major and completely reciprocal. Tall and slender ragweeds fail to completely neutralize their sites to western ragweed. For further explanation see Table IV.

However, these difficulties may yield to the assumption of quantitative differences in the content of different minor antigens in the different pollens.

Case 7.—Spri. was a resident of Chicago with hay fever of the late summer type of thirty years' standing, in later years running to asthma during August. He was able to avoid attacks by spending the season in Hot Springs, N. M., but in Prescott, Arizona, he obtained no benefit from the change of climate, he believed, on account of the presence of western ragweed, bur ragweed, Russian thistle and carelessweed.

By direct test (scratch) he reacted markedly to most pollens with which he was tested, representing all the major groups, also to dust and silk. All foods were negative. By intracutaneous test he reacted to animal danders, wool, flaxseed, Kapok, orris and several molds.

His serum sensitized by passive transfer to all pollens with which it was tested, but cat, dog and horse dander, orris, feather, Kapok and house dust sensitizations failed to transfer. When cross neutralizations were tried, it was found that western ragweed neutralized its sites to all pollens tested (Table VII) but its sensitization was neutralized completely only by short and bur ragweeds, and partly by tall and slender ragweeds, and sagebrush. Neutralization of sites by all other pollens left their activity unimpaired to western ragweed.

Western ragweed sensitization is, therefore, major and it is completely reciprocal with short and bur ragweeds. These two neutralize their sites to all other pollens of the ragweed group. Hence, their major antigens are

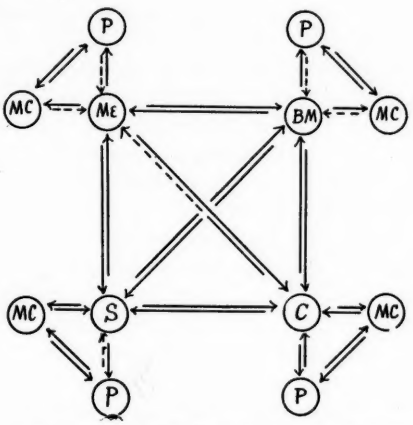

Fig. 10. Diagram showing cross reactions among some ragweed relatives with Spri. serum—marshelder, ME; burweed marshelder, BM; sagebrush, S; and cocklebur, C—and a comparison of their relations with the unrelated plantain, P, and mountain cedar, MC, showing that the ragweed relatives all contain a common minor antigen or antigens. They also all contain a minor antigen which is in plantain and one that is in mountain cedar. And mountain cedar contains an antigen which is in cocklebur and sagebrush but absent from marshelder and burweed marshelder. Plantain contains an antigen which is in cocklebur but absent from all the others.

alike but they may differ from western ragweed in their minor antigens since the short ragweed sensitization is neutralized, at least partially, by cocklebur and burweed marshelder, and bur ragweed sensitization is partly neutralized by burweed marshelder, while that of western ragweed is not. Tall ragweed only partially neutralizes its sites to western ragweed; however, it completely neutralizes them to all others of the ragweed group, and its sensitization corresponds exactly in its resistance to neutralization with that of western ragweed to all others tested. It thus appears that these four ragweeds, western, short, tall and bur, possess the same major antigen.

Sagebrush partly neutralizes the sites to the three true ragweeds and completely to all the other members of the ragweed group except bur ragweed, suggesting that it may possess the major antigen. However, its sensitization is neutralized by everything in the ragweed group and even by the unrelated mountain cedar, showing that its active antigen in this case is more probably a minor one.

Marshelder, burweed marshelder, cocklebur and sagebrush are all reacting through their minor antigens since they fail to neutralize to the major ragweeds and have their sensitizations neutralized by them. They

are all reciprocally neutralizing except that cocklebur only partially neutralizes the marshelder sensitization (Fig. 10). They are also closely related taxonomically but no more so than they are to the true ragweeds with which they are not reciprocally neutralizing. But that they are antigenically different seems to be shown by their interreactions with plantain and mountain cedar; marshelder and burweed marshelder are reciprocal with mountain cedar. They all neutralize their sites against these two pollens. But cocklebur is reciprocal with both; sagebrush is reciprocal only with mountain cedar; marshelder and burweed marshelder are reciprocal with neither. In view of the fact that plantain and mountain cedar are reciprocal with each other, this differentiation cannot at present be explained but may be due to quantitative differences.

Some significant facts emerge from these studies: Most allergic sera have a single major sensitization upon which all others depend. The homologous antigen of the major sensitization is capable of neutralizing all other sensitizations of the serum, however numerous, but the major sensitization cannot be neutralized by allergens of any but phylogenetically closely related species, presumably carrying the same major antigen. That a major sensitization among allergic sera is the rule seems certain because it was found in the seven sera reported on here, and these were selected for study only on their diversity of character, and the high degree and multiplicity of their sensitizations. Besides these, three other sera have been studied in some detail. Of one of them the major sensitization has been found to be carelessweed but of the others major sensitizations have not been found, but it has not been proved that they have none.

The major sensitization of a hay-fever patient appears to bear a definite relation to his past exposure. Thus Par. with major sensitization to sagebrush, Gip. to cedar, Rod. to Bermuda grass, and Spri. to ragweed, developed their hay fever in regions where these plants are prevalent causes of the malady. Boi., though a resident of California, where timothy and other grasses of his major sensitization are lacking, had become sensitized before taking up residence in California, either in Europe or the eastern United States, where such grasses are common causes of hay fever.

Only phylogenetically closely related species have been found to interreact reciprocally with that of the major sensitization. Thus we see the members of the genus Artemisia reciprocally neutralizing with sagebrush which, in turn, neutralizes unilaterally all other sensitizations of that serum. And we see the members of the genus Juniperus and the closely related Chamaecyparis reciprocally neutralizing with mountain cedar in the major position. Among the grasses reciprocal neutralizations with a major antigen do not extend throughout the whole family but only to a limited number of genera as, for example, timothy, orchard grass, perennial ryegrass, sweet vernalgrass, and more or less to redtop. The phylogenetic relationships of the grasses are not well understood. However, they are believed to be all unusually closely related for such a large family. With the exception of

Bermuda grass the results of these studies do not violate this conception. Bermuda grass, however, stands conspicuously apart from the other grasses. When it is in the major position it finds no reciprocals among the commoner hay-fever-grasses. And when other grasses are in the major position it is entirely minor, exhibiting no serological affinity with them more than with totally unrelated species.

Minor sensitizations are those that are neutralized by the major antigen, but whose corresponding antigens fail to neutralize the major sensitization. Like the major sensitization, they depend for their origin upon environmental stimuli, but they may or may not represent clinical sensitizations of the donor of the serum. Most of them will neutralize against each other either reciprocally or unilaterally. Which will and which will not neutralize against each other is quite independent of the taxonomic relationships and even of their other serological relationships.

The most plausible explanation of these phenomena is that the antigenic complex of the pollen cell has a mosaic structure similar to that ascribed by Landsteiner to animal and bacterial cells. While it is probably susceptible of analysis in the same way that the agglutinogens of Salmonella and typhoid strains of bacteria have been analyzed, the present observations enable one only to say that the antigenic complex of pollen grains consists of a major antigen which is specific, and a number of minor antigens which are only partly specific. The major antigen is shared only by the pollens of very closely related species such as those of the true ragweeds, or of timothy and orchard grass. But the distribution of the minor antigens is quite fortuitous, the same antigens occurring in the pollens from all groups of plants and, if reports of other investigators are well founded, even among allergens of animal origin.

SUMMARY

Pollen-allergic patients of the multiple sensitization type generally have a single major sensitization upon which the others all depend, no matter how numerous.

The pollen atopen has a mosaic structure similar to that of bacterial and animal cells, and is as susceptible of analysis. It consists of a major antigen which is species or group specific, being shared, if at all, only by phylogenetically closely related species; and it has a number of minor antigens which are common to related and unrelated species in an unpredictable way.

The minor antigens are capable of producing clinical symptoms.

It is a pleasure to acknowledge my indebtedness to Dr. Leon Unger, Dr. Albert Irving Clark, the late Dr. R. W. Lamson, and patients of their private practices for the sera used in these experiments.

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THE BEGINNINGS OF ALLERGY

A Reminiscence

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THE allergic diseases have been known to the medical profession for hundreds of years but have been unrecognized as such until the present century. When I began the study of medicine in the last years of the nineteenth century, Dr. Osler used to tell us that asthma was a nervous reflex contraction of the bronchial musculature due to irritation of the nasal mucous membrane by odors, often aggravated by the presence of polypi in the nose. Great emphasis was laid upon neurotic antecedents and nervous personality as etiological factors.

Although a quarter of a century earlier, in 1873, C. H. Blackley[4] in England had demonstrated that hay fever was due to the inhalation of grass pollens, and four years later Elias J. Marsh[25] in New Jersey had made pollen counts and related them to the severity of his own hay fever symptoms, their work had received but scant attention. The accepted theory was that the symptoms were due to irritation of certain spots of hypersensitiveness in the mucous membrane of the nose. These were searched for and cauterized, nasal spurs were sawed off, septal deviations were crushed and polypi were removed galore. Hay fever was a lucrative source of profit to the surgically minded rhinologist. The postoperative result was usually aggravated hay fever.

Urticaria and angioneurotic edema were believed to be vasomotor manifestations of an unstable nervous system, while migraine was exclusively in the domain of the neurologist, aided and abetted by the gynecologist. Eczema was "due to acid in the blood." Ménière's disease was the property of the otologist, and epilepsy—well, the best thing to do with an epileptic was to incarcerate him in an institution and forget him. Every one of these conditions was recurrent and believed to be incurable. While attacks might be alleviated, a permanent cure was beyond the expectations of the most optimistic.

The usual success in the handling of asthma at that period is illustrated by an experience of mine while resident physician in the Lakeside Hospital in Cleveland sometime between 1903 and 1905. Dr. John Lowman had his Western Reserve students on the wards for bedside teaching. I had a case of asthma for his clinic. After discussing the symptoms he turned to one of the students and said, "Mr. Blank, why do we advise change of climate in cases of asthma?" Mr. Blank, the son of a physician, looked the professor in the eye and said, "Because you can't do a damned thing for them and hate to see them hang around your office!" Dr. Lowman

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threw up his hands and said, "That is not what I expected, but I am afraid I will have to give you 100 per cent for that answer."

When in the fall of 1905 I began my work in London under Dr. Archibald Garrod, the leading pediatrist and medical chemist in England of his day, I took occasion to congratulate him on father's, Sir Alfred Garrad's, demonstration of the association between excess uric acid in the blood and gout. Dr. Garrod said, "It was a nice bit of work but I wish my father had never done it." On my asking why, he said, "For every gouty earl my father helped, thousands of patients with eczema, arthritis and what not have been allowed to suffer for years because both physicians and patients have been satisfied with the diagnosis 'acid in the blood.' There is excess of acid in the blood in gout and in no other disease. That diagnosis in all other conditions is the peg on which we hang the hat of our ignorance. When we discard that false tenet and begin to look for other causes of eczema and arthritis, then and only then will medicine make any advance in the control of those diseases."

During the first decade of this century, scientists were deeply interested in Theobald Smith's discovery of anaphylactic death in guinea pigs when he administered a second injection of diphtheria antitoxin. When Smith told Ehrlich of his findings, the latter had his assistant Otto[31] confirm and publish the results. In 1906, Roseman and Anderson[35] went one step further to prove that it was the horse serum, not the antitoxin element, which caused the death of the guinea pigs.

Among the other workers who devoted much time to the study of anaphylaxis in animals and to its relation to serum sickness in man were Von Pirquet and Schick[47] in Vienna, Paul A. Lewis[23] at the Rockefeller Institute in New York, and Gay and Southard[11] at Johns Hopkins.

When I returned from Europe in 1907 to the Rockefeller Institute, I found there my classmate and fellow medical house officer at Johns Hopkins, Dr. John Auer, working in the department of physiology under his father-in-law, Dr. Samuel Meltzer. Dr. Auer became interested in Dr. Lewis' work and, in conjunction with him, undertook an investigation of physiological aspects of anaphylaxis. With guinea pigs sensitized to horse serum, Auer and Lewis[1] demonstrated that anaphylactic death was due to asphyxiation, that, as the results were obtained when all nerve connections were severed, the phenomenon was the result of direct action on the bronchi, not through the central nervous system, and that anaphylactic death was due to tetanic constraction of the muscles of the walls of the bronchi, completely preventing the passage of air in or out of the lungs.

Important as were the findings of Auer and Lewis,[1] the epoch-making fact in connection with them was that Dr. Auer's father-in-law, in watching the guinea pigs die, was struck by the similarity between their symptoms and those of human beings suffering from bronchial asthma. When later in the year 1910 Dr. Meltzer[27] published his article expressing his belief

that bronchial asthma was a phenomenon of human anaphylaxis, he laid the foundation upon which has grown the science of allergy. The next year Eli Maschowitz,[26] in a review of anaphylaxis, grouped asthma, urticaria and eczema together and pointed out their relation to serum sickness. He also noted that all of them were accompanied by an eosinophilia.

Although Blackley[4] in the third quarter of the last century had scratched the skin of his arm, applied pollen thereto and obtained a wheal, the use of a scratch test was overlooked for forty years until Von Pirquet reintroduced it for the diagnosis of tuberculosis, and at the same time gave to the reaction the name of "allergy."

In 1910, Knox, Moss and Brown[21] at Johns Hopkins sensitized rabbits with horse serum and later injected 0.1 c.c. of a 10 per cent solution of horse serum intradermally into the skin of their ears and abdomen, and got swelling at the points of inoculation. Moss[29] then followed this by injecting horse serum intradermally into human beings as a test of susceptibility to serum sickness before administering antitoxin, and in a number of cases saw marked reactions.

The introduction of skin testing as a means of diagnosis, however, came with the observations of Oscar M. Schloss,[38] who had been a second year student when I was a house officer at Johns Hopkins. In 1912, Schloss, then teaching pediatrics at Cornell Medical College, published a preliminary report in which he cited the case of a child who had severe swellings of the mouth, tongue and lips whenever he ate eggs, oats or almonds. Using a Von Pirquet scarifier, he scratched the arm of the child and applied the offending substances. In a few minutes urticarial wheals appeared at the site of the scratches. He repeated the experiment with other foods and got negative results. He then made many experiments with the constituents of the foods and showed that it was the protein factor which gave the reaction. Clinical allergy had been born. It was, however, a sickly infant, and though receiving enthusiastic attention from its parent and a few of his friends, grew so slowly that it remained for a while quite unknown to the medical profession at large.

One friend, however, who showed great interest in Dr. Schloss' brain child was another pediatrist, Dr. Fritz Talbot[43] of Boston, who plunged avidly into the study of the new discovery and, in 1914, published a report[57] of six children suffering from asthma caused by egg who gave scratch tests to egg and were cured or greatly improved by the administration of capsules of egg albumin. In the same year J. G. Missildine[28] in Kansas reported two cases of horse asthma who reacted to skin tests with horse serum and were benefited by graded inoculations with horse serum. At about the same time, Goodale[12,13] of Boston had a series of cases of horse asthma in which he not only got reactions to diptheria antitoxin by skin tests but also by insufflating the serum into the patient's nostrils. The next year Goodale[15] reported attempts to desensitize his

horse asthma cases by spraying graded doses of diphtheria antitoxin into the nose and by giving it hypodermically.

After Oscar Schloss[39] read his paper, "Allergy to Common Foods," before the American Pediatric Society at Lakewood, N. J., on May 24, 1915, general interest in this new addition to our medical armamentarium spread rapidly among pediatrists but more slowly among internists and otolaryngologists. In 1915, R. N. Babcock[2] accepted the anaphylactic theory but believed that the chief etiological factor was focal infection and advised treatment with autogenous vaccines.

In 1916, Talbot[44] made the next great advance when, instead of using the crude flour or juices of the foods for testing, he began applying the pure proteins of the foods, hairs, et cetera, prepared by Dr. Wodehouse, and in the same year[45] read before the New England Pediatric Society a paper proving that protein could pass unchanged through the intestinal wall of infants during the first few weeks of life, thus explaining a probable source of sensitization. In the same year Schloss and Werthen,[40] by precipitin and anaphylactic tests of the urine, showed that a similar permeability to protein was present in older infants suffering from nutritional and gastrointestinal disorders.

At about this same time, C. J. White,[61] in an article in the *Journal of Cutaneous Diseases*, published a paper on the relation of allergy to eczema and the value of the skin tests, apparently the first dermatologist to admit that there was more to the treatment of eczema than the application of ointments. He deplored the tardiness of dermatologists in following the pediatrist in making use of allergic methods. In the same journal, McBride and Schorer[24] mentioned that urticaria may be due to sensitization to certain foods but omitted any mention of skin testing. Also in 1916, Blackfan[3] established the relation of eczema to allergy by testing a series of children with egg, cows' and human milk, ovomucoid, barley, horse serum, and beef extract. Of forty-three cases showing no clinical evidence of allergy, all were negative; of twenty-seven having eczema, twenty-two gave positive skin tests; in all other skin diseases the tests were negative.

At about this time I began to hear rumors of the work Dr. Talbot was doing in Boston and, after attending the Tri-City Pediatric Society in that city, I remained over another day and, on the strength of Dr. Talbot's having been in the class after mine at Harvard College, I met him at the Massachusetts General Hospital. He showed me the cases he had and demonstrated the method of testing. When we returned to his office, I went into further details. He told me that at that time he had eighty different proteins with which he was testing. When asked if it was necessary to have so many, he said it was to do the work adequately. Having in mind trying the new method on two charity cases at home, I asked how expensive the proteins were. He had just received five new extracts that day, and he tossed me the bill which accompanied them. When I read

"5 protein extracts, $300.00," I decided not to purchase eighty for two charity cases. I returned to Utica a disappointed and a wiser man and waited until the testing materials came on the market before starting on the road to becoming an allergist.

The following year Dr. Talbot came to Utica on my invitation to read a paper before the Section on Pediatrics of the Medical Society of the State of New York, of which I was chairman. While driving to my residence, Dr. Talbot remarked, "Utica! I think my father owns a store in this city, a gentlemen's furnishing store." As I looked puzzled, he said, "It is one of forty he owns in various parts of the country, none under his own name." When I suggested Wicks and Greenmans, our largest and most fashionable haberdashery, and he said, "Yes, that is it," I understood how Dr. Talbot was able to purchase eighty proteins at the rate of $300.00 for five. When I saw him a number of years later and asked him how he was getting along with his allergy, he said, "Oh, these chaps who are doing nothing but allergy have run me out of business. I have given it up and am devoting my whole time to pediatrics." He, however, had done more to make allergy a practical science than any other man of his day.

In the meantime a number of men were studying the problem of hay fever, turning back to the work of Blackley,[4] ignored and neglected for forty years, until Dunbar[9] resuscitated it in 1903. In 1909, Scheppergell[37] stated that hay fever was usually due to sensitivity to ragweed and attempted to desensitize his patients by spraying ragweed pollen into the nose. Two years later Noon[30] in England tested patient's susceptibility to grass pollens by instilling extracts of different concentrations into the eye. He judged the patient's sensitivity by the strength of pollen solution required to produce a slight redness of the conjunctiva. He then injected pollen solutions in increasing doses. He found that, whereas if he injected the pollen every three days there was little or no increase in the patient's resistance to it, if he gave the injections at from seven to ten-day intervals the resistance increased many hundredfold. Freeman[10] followed up Noon's work by showing that preseasonal injections of pollen greatly lessened the severity of the attacks.

In 1915, Goodale[16] and also Cooke[6] advocated the use of skin tests for the diagnosis of hay fever, Goodale using scratch tests while Cooke recommended intradermal tests and started a controversy which has continued to the present day. Cooke and VanderVeer[7] the following year showed that the ability to become sensitized was inherited. In 1916, Goodale[17,18] also published two papers on seasonal and perennial hay fever and advocated the theory that the chronic rhinorrheas and asthmas were usually of bacterial origin and should be treated with autogenous vaccines.

In the year 1917, as a result of a grant made by Mr. Charles F. Choat, Jr., of Boston, to the Peter Bent Brigham Hospital, for the study of

bronchial asthma, Walker[48-60] and Wodehouse[62,63] published a series of seventeen articles covering all aspects of the etiology and treatment of the disease and placed the science of allergy on a firm foundation.

From this time on, the recognition of allergy spread with ever-increasing speed, and additions to our knowledge came ever more rapidly. In 1918, Rackemann[32] divided asthma into extrinsic and intrinsic types. In 1919, Sutton[42] and Hannah[19] reported cases of ragweed dermatitis, and Cooke[8] added drug allergy to the list. In 1920, several observers including Rackemann[33] and Kern[20] called attention to the importance of house dust, especially mattress dust, as a cause of asthma. In 1922, Shannon[41] reported changes of disposition due to allergy, while Ratner[34] and Larsen and Bell[22] included rabbit hair among etiological factors. In 1924, Cadham[5] reported three cases of asthma due to grain rusts, and in 1927, Vaughan[46] definitely established the allergic origin of many cases of migraine.

During the third decade of the century the interest in allergy grew by leaps and bounds. Whereas the extensive bibliography in Rowe's[36] textbook gives but five articles on allergy written in 1914 and twenty-seven in 1920, in 1930, there were 163 and, in 1935, 317 articles on the subject. In 1923, the American Association for the Study of Allergy, with Dr. Grant Selfridge its president, and the Society for the Study of Asthma and Allied Conditions, under the presidency of Dr. Robert A. Cooke, were founded—two societies which remained rivals until the American College of Allergy was organized, when they combined under the name of the American Academy of Allergy. When in the autumn of 1929 the *Journal of Allergy* made its appearance with Dr. H. L. Alexander as the editor, allergy had attained the rank of a full-fledged specialty, and has been growing stronger ever since.

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HISTAMINE TREATMENT OF FOREIGN PROTEIN TYPE REACTIONS

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THIS paper is being presented because it is believed that the treatment of foreign protein type reactions by histamine has not been adequately reported. The following cases are reported because of the severity of the foreign protein reaction and dramatic relief of symptoms, both subjectively and objectively, in response to histamine therapy.

Horton[2] has long entertained the opinion that "The common denominator of allergic diseases, and some diseases not now recorded as being allergic in nature, is an underlying problem of edema provoked by local release of histamine or a histamine-like substance. In the skin, localized edema manifests itself clinically as urticaria and angioneurotic edema." He has reported the use of histamine as a therapeutic agent with marked success in many subjects. Following Horton's work, we have used histamine in patients with severe urticaria and angioneurotic edema, some of whom have failed to respond to other forms of therapy.

Sherman[3] stated that "Reactions indistinguishable from serum sickness, and with the same incubation period, are one of the most common manifestations of sensitization to penicillin of both amorphous and crystalline forms." This author further pointed out that penicillin sensitization is usually manifested by mild and transitory symptoms. At least one death has been attributed to an attempt to use penicillin in a patient who had previously showed evidence of sensitization (Barksdale[1]). With all of this we agree, except regarding the period of incubation of penicillin reactions, which may be decidedly longer than that ordinarily seen in serum sickness. We further feel that emphasis should be placed on occasional severe and often critical manifestations which may be resistant to ordinary therapeutic agents including antihistaminic drugs.

The following cases of foreign protein reactions present an adequate history with clinical signs, including those described by von Pirquet and Schick[5] in their monograph on serum sickness, such as urticaria, erythema, edema, itching, conjunctival hyperemia, and fever. In addition, we have one case presenting a toxic psychosis which has been observed previously by Strakosch.[4]

CASE REPORTS AND DISCUSSION

Case 1.—M. K., a thirty-one-year-old physician, entered the hospital at 10:00 a.m., May 12, 1947, complaining of urticaria, rash, edema and severe itching of two days' duration. Eight days prior to the onset of symptoms he had received oral penicillin for a urinary tract infection. The only other history of allergy was a mild attack of urticaria ten weeks previously, following an injection of penicillin in oil, for laryngitis.

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The patient was acutely ill and mentally confused. He appeared to be having a hard chill, and required several blankets. The oral temperature was 103.4° F. His skin was covered with typical urticarial wheals, and there was a generalized erythematous rash. There was marked swelling of the eyelids, and the whole face showed moderate swelling. The hands, feet and penis were markedly edematous. The conjunctivae were injected.

Intravenous histamine was started promptly on admission and gave immediate flush and relief of the chill, and many of the urticarial wheals disappeared. The patient went to sleep even though he remained disoriented. Pyribenzamine, which patient had taken of his own accord since his illness began, was continued in dosage of 50 mg. every three hours since the first hospital day without apparent results; epinephrine likewise was found to be ineffective.

During the next thirty hours he received four infusions of histamine; during this time he was definitely more comfortable and better oriented only during and for a few hours after the treatments. Furthermore, diuresis was definitely increased following the histamine, and it seemed that when an infusion coincided with a period of elevated temperature, the latter promptly subsided, although a precise relationship could not be found, since a spiking type of temperature may have been a part of the clinical picture anyway. In the hope, therefore, that if the histamine flush could be maintained constantly, more enduring improvement could be attained, a constant intravenous drip of histamine was begun at 10 p.m. on May 13. This gave continuous relief of symptoms and allowed the patient to sleep. On May 14 the edema had greatly subsided and the temperature remained normal for the first time. Except for occasional interruptions caused by the needle coming out of the vein, et cetera, histamine drip was continued for approximately sixty hours, and the patient remained comfortable after the infusion was discontinued. On May 16, histamine infusions were decreased to every six hours; itching occurred only three times during the night and then only for short periods; wheals appeared only once. On May 17 there was a little edema, and patient was out of bed for the first time. Histamine infusions were reduced to every twelve hours on May 18, and on May 19 the patient was discharged with no symptoms.

Case 2.—L. W. H., a thirty-five-year-old man, was admitted to the hospital August 26, 1947, presenting marked swelling of the right upper eyelid, generalized urticaria and edema of the face, hands, forearms, legs, back and buttocks of four days' duration. Two weeks prior to the onset of symptoms he had received three injections of penicillin in oil and wax. Aqueous penicillin eight months previously had caused no reaction.

There was no other personal or family history of allergy. Temperature on admission was 100° F. and rose to 101.4° F. the next day, after which it remained normal.

During the first two days of hospitalization, the patient received 50 per cent glucose intravenously, Benadryl, Pyribenzamine and epinephrine, with no results. On August 28, histamine acid phosphate (2.75 mg. in 250 c.c. of isotonic saline) was given every eight hours. Since this dosage did not cause appreciable flushing, the concentration of histamine was doubled on August 29. Improvement was immediate, particularly during and following the infusion, so that on August 31 the frequency of histamine administration could be reduced to every twelve hours. However, the patient seemed to develop a tolerance even to this double dose of histamine, but flush was restored after dosage was increased to three ampules (8.5 mg.) in each infusion. On September 3, 1947, he was discharged with no symptoms.

Case 3.—W. P. W., a fifteen-year-old white boy, was admitted to hospital October 2, 1947, for "hives" and loss of consciousness. Two years previously the patient

had received penicillin for pneumonia and developed urticaria. One week prior to the present illness, he received 300,000 units of penicillin in oil. On the sixth day he developed a generalized urticaria which did not respond to 200 mg. Pyribenzamine. The next day his urticaria was more intense and was complicated by nausea and vomiting, and he fainted one hour prior to admission. The patient was lethargic but responsive, and had a generalized urticarial rash and swelling of knee joints. The admission temperature was 100.2° F. Histamine intravenous drip therapy was started but with inadequate flushing; the second day the drug was doubled with only mild flushing. The temperature remained elevated until the last two hospital days. All symptoms had subsided on the eighth day of therapy, when he was discharged.

Case 4.—Mrs. E. A., a twenty-three-year-old white woman, was admitted to the hospital October 7, 1947. Penicillin one year previously had caused no allergic symptoms. Ten days prior to admission, she had received 300,000 units of penicillin in oil for chronic salpingitis. Two days prior to admission, she developed generalized pruritus and urticarial rash with edema of hands, face and feet, which did not respond to Benadryl. There was no record of previous allergic manifestations. Intravenous histamine drip was given with good flushing. On the third day of treatment the drug was decreased in time interval of administration because of subsiding symptoms. All lesions and symptoms subsided on the fourth hospital day. She was discharged on the fifth hospital day.

Case 5.—W. O. H., a twenty-year-old white man, was admitted to the hospital October 11, 1947, presenting generalized urticaria and painful joints. The patient had been well until October 1, 1947, when he received oral penicillin for pain in the right lower quadrant and a Neisserian urethritis. Symptoms developed the following day, including generalized urticaria, diffuse edema of face, hands and feet, and swelling and pain on motion of right knee.

After twenty-four hours of histamine therapy, all the urticaria had subsided; and there was only very slight swelling of the right knee on the third day, when he was discharged as improved.

Case 6.—N. S., a two and one-half-year-old girl, was admitted to the hospital December 10, 1947, presenting generalized giant urticaria and angioneurotic edema. On December 4 she had been given 300,000 units of penicillin in oil and wax, a sulfonamide mixture, aspirin, and phenobarbital for tonsillitis. Fever continued, and on December 8 she again received 300,000 units of penicillin in oil and wax, and it was again given December 9 because of a questionable culture. The patient was given a skin test dose of undiluted diphtheria antitoxin, and within fifteen minutes she developed a severe, giant urticaria. As antitoxin was thought dangerous, penicillin (25,000 units in saline every three hours) was given for the treatment of diphtheria; Pyribenzamine, epinephrine, ephedrine, and amytal were given for itching, urticaria and edema without effect. Intravenous procaine was tried one time without improvement. Because of the age of the patient, intradermal injections of histamine dihydrochloride were started immediately after hospitalization. Five hundredths of a cubic centimeter of 1:1000 dilution was selected as the optimum dose, and was given every two hours for fourteen hours with continuous vigorous flushing, and with disappearance of all symptoms at the end of this time. Within three hours after intradermal histamine had been started, the temperature of 105° F. (rectal) had dropped to normal, diuresis had been established, and the child had passed from restlessness to quiet sleep. Inasmuch as penicillin was continued without further reaction we believe the allergic reaction is an example of an immediate re-

TABLE I

Patient	Size of Dose of Histamine	Frequency of Treatment	Duration of Treatment	Duration of Symptoms Before Treatment	Incubation Period
M. K.	(a) 2.75 mg. HAP* in 250 c.c. N.S., I.V.	q. 6. h.	2 days	2 days	8 days
	(b) 16 ampules HAP each in 250 c.c. N.S.	continuous	60 hours		
	(c) 2.75 mg. HAP in 250 c.c. N.S., I. V.	q. 6. h.	2 days		
	(d) same	q. 12. h.	1 day		
L.W.H.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	1 day	24 days	15 days
	(b) 5.5 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	2 days		
	(c) same	q. 12. h.	1 day		
	(d) 8.25 mg. HAP in 250 c.c. N.S., I. V.	q. 12. h.	1 day		
W.P.W.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	1 day	1 day	7 days
	(b) 5.5 mg. HAP in 250 c.c. N.S., I.V.	q. 6. h.	1 day		
	(c) same	q. 8. h.	1 day		
	(d) same	q. 12. h.	5 days		
Mrs. E.A.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	2 days	2 days	10 days
	(b) same	q. 12. h.	3 days		
W.O.H.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 6. h.	3 days	9 days	1 day
N.S.	(a) HAP 2.75 mg./5 c.c. 0.1 c.c. I.D	q. 1. h.	4 hours	24 hours	immediate
	(b) Histamine 1/1000 0.05 c.c. I.D.	q. 2. h.	14 hours		
H.S.T.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	2 infusions	27 days	immediate
	(b) 6 ampules HAP each in 250 c.c. water	continuous	8 hours, could not be repeated because of edema.		
	(c) HAP 2.75 mg./c.c.				
	0.1 c.c. I.D.	q. ½. h.	4 hours		
	0.5 c.c. I.D.	q. ½. h.	1½ hours		
	0.7 c.c. I.D.	q. 1. h.	3 hours		
	(d) Histamine 1/100 0.1 c.c. I.D.	q. 2. h.	2 days		
W.E.K.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 6. h.	2 days	2 days	8 days
	(b) 5.5 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	1 day		
	(c) HAP 2.75 mg./c.c.	q. 2. h.	1 day		
	0.2 c.c. I. D.	q. 2. h.	1 day		
H.O'R.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	3 days	3 days	11 days
	(b) Histamine 1/1000				
	0.2 c.c. I.D.	q. 2. h.	2nd day †		
	0.3 c.c. I.D.	q. 2. h.	3rd day †		
	0.4 c.c. I.D.	q. 2. h.	1 day		

*HAP — Histamine acid phosphate
† Given in conjunction with I.V. therapy on 2nd and 3rd day.

action to a diphtheria antitoxin dose, manifested by severe edema and urticaria. Because of the age of the child it was not thought advisable to attempt intravenous administration.

Case 7.—H. S. T. was admitted to the hospital January 21, 1948, complaining of intense itching, redness and edema of the entire body. Oral penicillin one year previously had given no ill effect. He had received oral penicillin, two tablets, for a sore throat on December 26, 1947, and within a few minutes began to itch and soon developed a generalized edema and swelling of the tongue. Epinephrine and Bena-

dryl were given with decreasing relief. Three days prior to admission he developed generalized edema and oliguria. During this time he substituted Pyribenzamine for Benadryl without benefit. Previous allergy to sulfonamides was manifested by generalized edema in 1936.

The patient appeared critically ill, with generalized urticaria and edema; a few dry, crackling râles were heard around an old thoracotomy scar on the right thorax. Intravenous histamine was started immediately and repeated in eight hours with moderate flushing; in view of extensive edema distilled water instead of sodium chloride was used as a vehicle. The patient obtained relief of symptoms while receiving the infusion and for two hours afterwards. After twelve hours constant infusion was started and was continued for eight hours, during which time six ampules of histamine were administered, relief being noted only while the infusion was being given. By this time edema had progressed so that veins could no longer be found, and intravenous infusions had to be discontinued. In view of this, the intradermal route seemed to offer the only route of administering the drug. At first 0.1 c.c. of 2.75 mg. histamine acid phosphate per c.c. was given every half hour for four hours; only a slight flush was obtained, with little relief of itching. The amount of drug was then raised to 0.5 c.c. every half hour for three doses with little increase in flushing. Dosage was then raised to 0.75 c.c. every hour for three hours; the flush obtained lasted only about one-half hour. Histamine dihydrochloride (1:100) was then substituted, 0.1 c.c. being given every two hours for two days, with the result that a continuous flush was maintained. In spite of free fluids by mouth as well as the infusions, the urinary output was nil for the first twenty-four hours in the hospital, and was only 480 c.c. on the second day, with marked increase of generalized edema. As soon as adequate flushing was obtained, diuresis was prompt, and the urticaria and edema began to subside.

We believe that after an adequate technique for intradermal histamine administration was established in this case, the results were much more spectacular than from the intravenous route. Certainly the intradermal method afforded therapeutic action of the drug without the risk of continuing intravenous fluid in presence of the increasing edema. The patient was discharged as recovered on January 26.

Case 8.—W. E. K., a thirty-nine-year-old man, was admitted to the hospital January 26, 1948, for an appendectomy. A gangrenous appendix was removed, and penicillin crystals were put in the wound at the time of the operation. Seven days after the appendectomy, a hemorroidectomy and fistulectomy were performed. The following day, the patient developed a severe, generalized, giant urticaria with angioneurotic edema of the face and extremities and intense itching with rise in temperature to 101.8° F. He had no other allergies; however, one month previously he had received eighteen tablets of penicillin (50,000 units each) for a chest cold. The patient was treated for two days with epinephrine. Pyribenzamine, Benadryl and intravenous 50 per cent glucose, with no effect except aggravating the symptoms. On February 5, histamine infusions were started, producing a good flush with relief of symptoms during the infusion and for thirty minutes thereafter. This patient received intravenous histamine every eight hours for three days with good results. At the end of this period, intradermal therapy was substituted because intravenous injections were objectionable to him. A continuous flush was maintained on 0.2 c.c. of 2.75 mg. per c.c. of histamine acid phosphate intradermally. A clinical cure was obtained.

Case 9.—H. O. R., a forty-year-old man, entered the hospital February 11, 1948, complaining of "hives," severe itching and edema. A generalized giant urticaria, with some wheals ten inches in diameter, was present. There was massive edema of

face, extremities, buttocks, both knees and wrists. Two years previously, aqueous penicillin had caused a slight rash which was controlled with epinephrine. Two weeks prior to this admission, he had received three daily injections of penicillin in oil and wax (300,000 units) for a "chest cold." Eleven days later he developed his present symptoms. Pyribenzamine, 50 mg. every four hours for two days, had given no relief, but seemed to aggravate the discomfort. Temperature on admission was 99.8° F., rose to 102° F. for the next two days, and then returned to normal.

On admission 2.75 mg. histamine acid phosphate in 250 c.c. isotonic saline was administered intravenously and was repeated for three days. On the third day it was decided to supplement the infusion with intradermal therapy every two hours of 1:1000 histamine dihydrochloride, starting with 0.2 c.c. On February 14, intravenous infusions were discontinued and the intradermal injections were increased to 0.4 c.c. every two hours. The patient was comfortable as long as he was flushed, but only slight objective improvement was noted. On the fourth day, some urticaria and edema of the right hand and ankle persisted. On his last hospital day he showed no urticarial lesions and minimum edema of ankles. The patient was discharged as improved but with slight residual ankle edema on February 15.

METHOD OF ADMINISTRATION

Intravenous administration of histamine is the method of choice, in that the dosage can be controlled, and undue side effects can be terminated upon discontinuing the therapy. Dosage of 2.75 mg. histamine acid phosphate in 250 c.c. isotonic saline or 5 per cent glucose in water is given for the first infusion to determine the sensitivity of the patient. The rate of the infusion is regulated to a speed sufficient to just produce a generalized flush; if given too rapidly, a severe headache and substernal pain are encountered.

At first, we followed the technique advocated by Horton,[2] giving the infusions twice daily; but we soon found improvement was not uniformly sustained in the interval between infusions. Consequently, we have tried various intervals. We believe that the average patient does better with injections up to every six or eight hours. In our one case of extreme severity, continuous administration was necessary. When signs have disappeared, or are minimal, the infusions may be reduced to every twelve hours and eventually every twenty-four hours.

When rapid administration of the above dosage does not produce a generalized flush of the skin, the histamine acid phosphate may be increased to 5.5 mg. in 250 c.c. of vehicle.

Intradermal administration has been used when veins were obscured by edema, or in the presence of small veins, and when intravenous therapy did not give a maintained flush, and in children. This method has to be tried with caution as therapy cannot be discontinued at will. Small intradermal injections, ranging from 0.1 c.c. of histamine acid phosphate, 2.75 mg. per 5 c.c., to 0.75 c.c. histamine acid phosphate per 1 c.c. have been given. When larger quantities are required, histamine dihydrochloride 1/100 has been given in injections of 0.05 c.c. to 0.1 c.c. The dose is determined by the body flush. The dose that will produce a flush is that sought for. The flush of each dose is maintained from one-half to two hours.

In all cases treated with histamine there has been subjective relief; in two cases relief was spectacular. Some objective relief has been obtained when adequate flushing was established. There were no ill effects noted from prolonged intravenous administration. Headaches during administration have always subsided when the infusion was discontinued.

SUMMARY

Nine patients with severe foreign protein type reactions, most of whom have failed to respond to other forms of therapy, have been treated with intravenous or intradermal histamine. In all there was clinical improvement. No definite dose or rate of medication can be established; each patient must be treated individually.

Histamine has a definite place in the treatment of severe foreign protein type reactions.

The allergic reactions resulted from penicillin in eight cases, and from horse serum in one.

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A CLINICAL EVALUATION OF A NEW ANTIHISTAMINE AGENT "TRIMETON"

A Conjoint Study of 227 Patients

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THE clinical evaluation of any drug, although often entered into lightly, is nevertheless a most complex study. No two patients are alike. None suffers from exactly identical conditions under circumstances in any way similar. At the worst, each patient reports an entirely different version of the effects, in infinite variety. At the best, however, there is some underlying consistency which may help other physicians learn what can be expected from the use of the new medication. The data are not susceptible to mathematical analysis, except superficially and on a percentile basis.

For the purposes of this investigation, Trimeton* was distributed to the staff physicians of The Allergy Clinic of The Boston Dispensary for use in the clinic, their private practices and the separate additional clinics of which they were either chief physicians or assistants. In all, Trimeton was used by over 300 patients. Of these, seventy could not be tabulated for statistical purposes. This group includes patients who took trips, were hospitalized for conditions as varying as appendectomies and babies, suffered intercurrent illnesses, as well as those who, having received medication for symptomatic treatment, never returned to report their progress. A few of these patients were not to be trusted for adequate reports for any medications, and others were taking so much other medicine that the exact effects could not be ascertained. The 227 who remain represent both sexes and all ages from six to seventy-two, as homogenous a population as can be chosen from private and clinic practice. Such irregularities as occur are balanced by the fact that all types of patients are represented as seen by twelve physicians in five public clinics and in private practice.

The Trimeton (prophenpyridamine) was available in tablets (25 mg.). Almost all of the patients took one-half tablet three or four times daily, although some achieved excellent relief with one-quarter tablet. A few took one whole tablet, and several, two tablets, four times daily.

Trimeton differs from other antihistaminic agents in not being a derivative of ethanolamine or ethylenediamine. The chemical characteristics, the acute and chronic toxicity studies, and the antihistaminic action of Trimeton as well as comparisons with Benadryl and Pyribenzamine, both *in vitro* and *in vivo* with mice, rats, dogs, and guinea pigs have been dwelt upon separately.[1,2,3]

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This study was made by the staff of The Allergy Department of The Boston Dispensary, especially Dr. I. Alan Annis, Dr. Joseph H. Kaplan, Dr. Harry Korb, Dr. Joseph P. Maher, Dr. Conrad Nobili, Dr. Paul P. Norman, Dr. Russell C. Norton, Dr. Anna J. Reinauer, Dr. Sylvia Ruby, Dr. Theodore Sannella and Dr. L. Robert Weiss.

*Trimeton was supplied through the courtesy of the Schering Corporation, Bloomfield, N. J.

The patients studied can be classified in the following syndromes: allergic coryza, vasomotor coryza, bronchial asthma, atopic eczema, urticaria, angioneurotic edema, contact dermatitis, acute coryza, migraine, exfoliative dermatitis, radiation sickness, acne rosacea, generalized pruritus and various combinations of the above, two or three conditions sometimes being present in the same patient.

The largest group was represented by the patients with inhalant nasal allergy, usually due to pollen, but also to house dust and other inhalants, sufficiently constant in their presence to permit the use of the subject for purposes of study. Of the ninety patients, sixty-two reported excellent relief, meaning complete, or almost complete, freedom from symptoms. Nineteen demonstrated moderate, although satisfactory, relief, and nine, no relief whatsoever. In seventy patients, there were no side reactions of any type. In twelve, the side reactions were manifested as slight drowsiness. In seven, the side reactions were reported as moderate, and in one, as severe.

Of special interest is the all-or-nothing type of response, seen in this and other groups described below. In five of nine patients reporting no symptomatic effect, there were no side reactions. One who had had no relief suffered a most severe reaction, marked by nausea, swollen eyelids and urethral irritation, reacting similarly, but with additional numbness and tingling, to Benadryl, Pyribenzamine and to Decapryn. Another with no effect on his symptoms had had none from either Benadryl or Pyribenzamine. One patient with excellent results reported dizziness when Trimeton was taken on an empty stomach. Eight patients having excellent results noted slight drowsiness and one a dryness of the nasal membranes. One patient suffered from a mild, transient amnesia and another from "crankiness and irritability." In all, however, in only eight patients of the ninety was it necessary to stop the medication for its side reactions.

The second largest group were the patients diagnosed as cases of vasomotor coryza. The condition was defined as a non-infectious, non-allergenic nasal coryza, characterized by a pale, boggy mucosa and symptoms which were non-environmental and non-seasonal in nature. The skin tests were negative. Of the twenty-six patients in this group, constant in symptomatology and recalcitrant to almost all previous treatment, eleven reported excellent and seven, good relief. In eight there was no effect in doses up to one tablet four times daily. In twenty-three there were no reactions. Mild drowsiness occurred in two patients and moderate drowsiness in one.

Since these patients represent a group which uses medication locally and orally of the greatest variety and amounts, the reports are worthy of detailed description. Seven showed an all-or-nothing response with no relief and no side reactions. One of these achieved good relief with Decapryn. The subject, who reported moderate drowsiness, suffered similarly from Decapryn and Benadryl. Of those reporting moderate relief, one preferred Pyribenzamine and one Decapryn. One, who re-

ported excellent relief and no side reactions, had had no relief and severe side reactions from both Benadryl and Pyribenzamine, and another had reacted violently to Pyribenzamine. Two, who had fair relief, stated that Trimeton was equal in efficacy to Pyribenzamine.

The next largest group was represented by the patients with bronchial asthma, in all, twenty-five, with pollen or other inhalant allergy, seasonal or environmental and not associated with upper or lower respiratory tract infection. Of these, fifteen suffering from mild wheezing reported excellent relief, five, moderate and five, no relief.

Mild reactions occurred in five and moderate drowsiness in one. Of the mild reactions, one was "ringing in the ears"; one "slight dryness of the mucous membranes" (also caused by Benadryl); and one "rusty taste in mouth" (better relief and no side reactions from Luasmin capsules). One patient reported nausea on three occasions and one was drowsy. Three of the patients who reported excellent results and no side reactions, took, however, supplementary medication which, alone, did not keep them satisfactorily symptom-free.

In an additional group of eight patients suffering from bronchial asthma, associated with sinus or lung infection and marked by an absence of skin tests or ascertainable allergy, three, to our surprise, achieved excellent, and one, moderate relief. Two of the former and one of the latter required additional medication, itself not sufficient to clear symptoms. In four there was no change. In none of this group, small as it was, were there any side reactions, although two of the patients took doses of two tablets four times daily, a total of 200 mg. in twenty-four hours.

Of the total number of patients studied, twenty-two had simple urticaria; two, angioneurotic edema; three, urticaria and angioneurotic edema, and one, urticaria and contact dermatitis. Of the simple urticaria patients, fifteen reported excellent, that is, complete relief; three, moderate relief, and four, no relief whatsoever. Reactions for the entire group totalled two, one of these being mild, and one, severe. The mild reaction was drowsiness, also caused by Pyribenzamine, Benadryl, and Decapryn. The severe reaction occurred in a patient who had no relief and was demonstrated by both nausea and drowsiness. In two of the patients, the pruritus was relieved but not the wheals.

Thirteen of these twenty-two patients had had other antihistaminic agents and their reports show how difficult it is to evaluate the antihistaminic group of drugs. One patient found Trimeton better than any other antihistaminic; and in another, the Trimeton not only cleared the hives but permitted the patient to eat interdicted foods. Two patients, who had partial relief on all other antihistaminics, were completely relieved with Trimeton. One patient, however, who had no relief with Trimeton was helped by Pyribenzamine, and another, who had no relief with Trimeton, was completely relieved by Decapryn. A patient, almost completely re-

lieved with Decapryn, was completely cleared by Trimeton; one patient found Trimeton and Decapryn equally efficacious; one patient, moderately relieved with Trimeton, was completely free of urticaria with Decapryn; and another, who achieved excellent results with Trimeton with no side reactions, had severe drowsiness when using Neo-antergan.

There were two patients with angioneurotic edema, one of whom was moderately relieved and the other not relieved. Neither had side reactions. Neither was relieved by any other antihistaminic agent. On the other hand, in three patients with urticaria and angioneurotic edema, all three showed complete relief; none of the three showing side reactions. One was equally relieved with Decapryn. One patient, who suffered from contact dermatitis (poison ivy) and urticaria, showed an excellent response and no side reactions with a marked diminution of all of his pruritus.

Seven patients with atopic eczema were given Trimeton for symptomatic relief of the pruritus. In three there was excellent relief; in three there was moderate relief; and in one there was no effect. The last patient had an associated fungous condition, the pruritus being unaffected by any other agent. One of the patients with moderate relief had less pruritus when taking Pyribenzamine. None of the patients in this group showed any side reactions.

General pruritus was complained of by three patients. Of these, two achieved excellent and one, no relief. None showed side reactions. The patient who was not relieved, has shown no relief from any other medication.

One patient with acute coryza found immediate relief lasting four to six hours with no side reactions; two patients with contact dermatitis had excellent relief of their pruritus with no side reactions. One patient with acne rosacea associated with flushing and pruritus had no relief and no side reactions. Of the three patients with exfoliative dermatitis associated with pruritus, two were completely relieved with no side reactions. One was moderately relieved, although he suffered slight drowsiness. He had no relief with Pyribenzamine.

Of two patients, suffering from radiation sickness, one showed excellent relief, and the other was moderately relieved. Neither suffered side reactions. Two patients with typical migrane were completely relieved of their symptoms; one with no reaction and the other with a mild drowsiness.

There was a group of twenty-one patients, showing a mixed syndrome of hay fever and bronchial asthma. Of these, eleven reported excellent results; four, moderate results; and six, no effect. The reactions were elicited as none in seventeen, and moderate in four. Six of these patients reported that the medication was excellent for their hay fever and only partially affected their bronchial asthma. One patient was relieved of the symptoms of both syndromes on two tablets (50 mg.) four times daily. One patient, who had no effects and no reactions, was relieved by Luasmin capsules. The reactions were listed in one patient as nervousness, irritability and unsteadiness; in another, as dryness of the mouth; and a third and

fourth, as slight drowsiness. One patient took additional medication which alone was not effective, but with Trimeton gave him excellent relief with no side reactions.

There were three patients suffering from hay fever, bronchial asthma, and atopic eczema, of which the bronchial asthma was quiescent in two. All three reported excellent results with no side reactions, the third patient being relieved of the nasal, bronchial and dermatological symptoms.

Two patients presented the mixed syndrome of hay fever and urticaria. Both reported excellent results, one with no reactions and one with moderate drowsiness.

In an additional two patients, hay fever and atopic eczema were coincidentally present. In neither were there side reactions, although in one there was excellent, and in the other, moderate relief. There was one patient with bronchial asthma and urticaria, who was relieved of both syndromes, being completely symptom-free while taking the medication and showing no side reactions. The relief for the urticaria was longer lasting than for the wheezing.

In total, the 227 patients presented twenty allergic and nonallergic syndromes, alone or combined. Of these, there was complete alleviation of the presenting symptoms in 140 and moderate relief in an additional forty-eight, a total of 83 per cent. In thirty-nine there was negligible effect. Side reactions appeared as slight in twenty-one (9 per cent); moderate in fifteen (6 per cent); and severe in two (less than 1 per cent).

SUMMARY

In summary, Trimeton, a new antihistaminic agent, was used in the treatment of 227 patients seen in routine public and private practice. Of these, 61 per cent were completely symptom-free and an additional 22 per cent moderately comfortable. Of those with hay fever, 90 per cent were relieved; with urticaria, 81 per cent; and with mild extrinsic bronchial asthma, 80 per cent. Of the side reactions, chiefly drowsiness, which appeared in 16 per cent of the patients, in 9 per cent this permitted the continuation of the use of Trimeton, leaving only 6 per cent in whom the drug could not be continued.

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STUDY OF A NEW HISTAMINE ANTAGONIST

(2-Methyl-9-Phenyl-2, 3, 4, 9-Tetrahydro-1-Pyridindene Hydrogen Tartrate)

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A NEW ERA dawned in the treatment of allergic disorders when Fourneau and Bovet, in 1933, showed that certain phenolic ethers are effective antagonists of histamine, the pathological release of which is thought to result in allergic symptoms. Soon, other compounds, having the ethylenediamine radical, were studied and this led to the quest for better drugs of this type.

In this country, two compounds were introduced: namely, beta-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) and N,N-dimethyl-N'-benzyl-N'-(alpha-pyridyl)-ethylenediamine monohydrochloride (Pyribenzamine). Feinberg,[1] presenting an excellent review on the experimental and therapeutic status of antihistaminic agents, commented with regard to Benadryl and Pyribenzamine that "both drugs give a high incidence of side reactions, among which sedation and drowsiness are most commonly observed." Thus, there is a place for an effective antihistaminic drug which is distinguished by a lower frequency or lesser intensity of toxic reactions. With this in mind, we have undertaken the clinical evaluation of a new compound submitted to us by Hoffmann-La Roche, Inc., originally under the designation of NU-1504, and later under the name of Thephorin.*

The drug under consideration is 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate and has the structural formula shown in Figure 1.

A comparison with the formulas of Benadryl and Pyribenzamine, also given in Figure 1, shows that Thephorin belongs to a different class of compounds.

The pharmacology of Thephorin has been explored by Lehmann[2] who demonstrated that it is very potent in antagonizing important physiological effects of histamine on smooth muscle, on arterial pressure, and on capillary permeability.

CASE MATERIAL

Thephorin was used in the treatment of 140 ambulatory patients whose complaints were either proved to be due to an allergy, or were of a presumably allergic nature. There were fifty-three males, ranging in age from two and one-half to seventy-nine years, and eighty-seven females whose ages ranged from four and one-half to seventy-one years. The types of cases included nonseasonal vasomotor rhinitis; hay fever; asthma, of the

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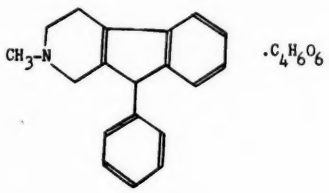
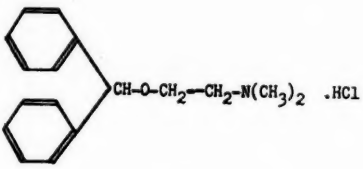
*Roche brand of phenindamine.

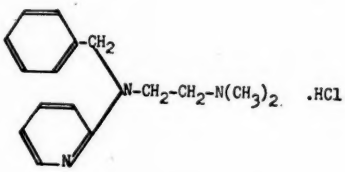
chronic and seasonal variety; various cutaneous allergic manifestations; and miscellaneous conditions. From Table I, listing separately each of the different allergic manifestations encountered, it can be seen that the 140



Thephorin



Benadryl



Pyribenzamine

Fig. 1

TABLE I. SUMMARY OF TYPES OF ALLERGIC MANIFESTATIONS IN 140 PATIENTS TREATED WITH THEPHORIN AND OF THEIR RESPONSES

Types of Allergy	Number of Instances	Number Benefited	Number Not Benefited
Nonseasonal vasomotor rhinitis	68	55	13
Hay fever	37	31	6
Asthma	31	18	13
Allergic conjunctivitis	4	1	3
Urticaria	7	6	1
Urticaria with erythema multiforme	1	1	
Angioneurotic edema	2	1	1
Neurodermatitis	5	3	2
Contact dermatitis	4	2	2
Exfoliative dermatitis	1	1	
Penicillin sensitivity	1		1
Migraine	3		3
Histamine headache	1	1	
Abdominal migraine	2	1	1
Ménière's syndrome	1		1
Aphthous stomatitis	1	1	
	169	122	47

patients showed a total of 169 allergic symptoms. In 105 instances, the patients suffered from a nasal allergy. Next in frequency were instances of asthma (thirty-one cases). The other allergic manifestations were represented by only small numbers.

TABLE II. SUMMARY OF RESULTS AND SIDE EFFECTS IN 140 ALLERGIC PATIENTS TREATED WITH THEPHORIN

No. of Cases	Results				Total No. Improved
	Excellent	Good	Fair	Negative	
140	60(42.9%)	37(26.4%)	9(6.4%)	34(24.3%)	106(75.7%)

No. of Cases	Side Effects				
	Mild	Moderate	Severe	Total	None
140	13(9.28%)	23(16.4%)	18(12.8%)	54(38.6%)	86(61.4%)

PROCEDURE

After a complete medical examination which, in many instances, included skin testing, Thephorin medication was instituted. The preparation was given orally in the form of 25 mg. tablets or syrup containing 10 mg. of Thephorin to the fluid dram. The syrup was used chiefly in children but occasionally also in the adult for better flexibility of dosage. Therapy was initiated with small doses: 25 mg. one to three times a day for adults, and 10 mg. at similar intervals for children. If no relief was obtained, the initial dose was increased until the patient derived benefit from the medication or until side reactions appeared. There were subjects who tolerated 400 mg. a day without untoward effects. Generally though, symptoms were controlled in adults by a total daily dose of 50 to 150 mg., and in children, depending on age, by correspondingly smaller doses. The number of treatment days ranged from one to 156 with an average of eighteen days. The maximum amount of Thephorin ingested by one patient was 6,400 mg., and this was taken in two courses of eleven and twenty-one days with a medication-free interval of twenty-five days. On an average, each patient received 1,281 mg.

If side effects occurred, medication was usually stopped; measures other than discontinuation of the drug were never required. However, frequently the patients would rather bear with an untoward reaction than forego the benefit afforded by Thephorin. In these cases, medication was continued in spite of side effects, particularly if these were of a mild nature.

RESULTS

Thephorin gave relief to 106 patients (75.7 per cent), and thirty-four patients (24.3 per cent) were not benefited. A patient was counted as relieved if the degree of improvement derived from the drug warranted its continued use. As appears from Table II, listing the degree of the success attained and the intensity of side effects, both in relation to numbers of patients, results were excellent in almost 43 per cent of the cases studied.

Nonseasonal Vasomotor Rhinitis.—Thephorin produced relief in fifty-five out of sixty-eight patients, an incidence of 81 per cent. Results were

excellent in thirty-three (49 per cent), and only thirteen (19 per cent) were not benefited.

Hay Fever.—Thephorin helped thirty-one (84 per cent) of the thirty-seven cases. Excellent relief was experienced by eighteen (49 per cent) and only six (16 per cent) were not improved.

Thus, in nonseasonal and seasonal allergic rhinitis, almost half the patients obtained excellent relief from Thephorin. Speculum examination proved objectively the shrinking of the congested nasal mucosa, sometimes within one half hour after the initial dose. It is worthy of note that two patients who for years had been completely dependent on nose drops for relief of nasal blocking, substituted Thephorin effectively for the local treatment.

Asthma.—Eighteen of the thirty-one asthmatic patients (58 per cent) obtained some degree of benefit from Thephorin, and thirteen (42 per cent) were not improved. Thus, the incidence of success was less than in the rhinitis cases. Moreover, the degree of relief was only moderate, with not more than six patients (19 per cent) experiencing excellent results. Generally, seasonal asthma was more amenable to treatment than chronic asthma.

Various Other Allergic Conditions.—All other allergic manifestations were treated in such small numbers that the percentage expression of results would be meaningless. The general trend of responses is shown in Table I.

It can be seen that three of the four patients with allergic conjunctivitis were not relieved. However, an excellent result was obtained in a nine-year-old boy who developed ophthalmic symptoms during the tree and grass season. Skin tests for pollens were negative, but eye tests were positive. The patient experienced relief within thirty minutes after the intake of Thephorin. Because of the severity of symptoms, he was given 25 mg. three times a day for two days. This dosage was then reduced to 25 mg. on a p.r.n. basis.

Of the seven cases of urticaria, six derived some degree of benefit. Thus, the further use of Thephorin in urticaria seems certainly warranted. Of the two cases of angioneurotic edema, treatment was attended by excellent results in one, and it was a complete failure in the other. Similarly, Thephorin helped three of the five cases of neurodermatitis and two of the four patients with a diagnosis of contact dermatitis. The case of exfoliative dermatitis was that of a woman, aged fifty-eight, who had been studied and treated both at the University Hospital and the Jewish Hospital. Her intractable pruritus responded well to Thephorin.

The three cases of migraine failed to derive any benefit. The one patient with a diagnosis of histamine headache was well pleased with the relief

afforded him by Thephorin. Pyribenzamine and Benadryl had succeeded also in this case. The patient now uses Thephorin during the day and Benadryl in the evening because of the concomitant sedative-hypnotic effect of the latter drug.

TABLE III.—FREQUENCY DISTRIBUTION OF SIDE REACTIONS OCCURRING IN 140 ALLERGIC PATIENTS TREATED WITH THEPHORIN

Side Effects	Occurrence in Number of Cases
Insomnia	30
Nervousness	12
Flushes	6
Perspiration	6
Urinary symptoms	5
Palpitation and tachycardia	4
Dizziness	4
Nausea	4
Anorexia	4
Depression and drowsiness	4
Mental stimulation	3
Chilliness	3
Dryness of nose and throat	3
Headache	2
Weakness	2
Heartburn	2
Abdominal cramps	2
Decreased libido	2
Tremor	2
Chest oppression	1
Sighing respiration	1
Flatulence	1
Fever (99.6°)	1
Total	104

The patient with Ménière's syndrome remained unrelieved by Thephorin. Pyribenzamine and Benadryl had also failed to relieve this patient.

The patient exhibiting aphthous stomatitis was sensitive to tomatoes, as proved by skin testing. When placed on Thephorin, the ulcers disappeared in one or two days, whereas they lasted one or two weeks without the antihistaminic medication.

SIDE EFFECTS

From Table II, it appears that side effects occurred in fifty-four persons (38.6 per cent) and that these were severe in eighteen (12.8 per cent) of the subjects treated with Thephorin. Many patients complained of more than one reaction. Thus, a total of 104 side effects occurred in the fifty-four subjects experiencing untoward symptoms. It appears from Table III, listing the various reactions in the order of their frequency distribution, that insomnia was the most commonly encountered symptom. Another not infrequent effect on the central nervous system was a state of undue excitability described by the patients as "jitteriness," restlessness or irritability, and grouped together in Table III under nervousness. Other

neurological manifestations included mental stimulation, dizziness, weakness, chilliness, diminution of libido, depression and drowsiness.

Five patients complained of urinary symptoms; viz., retention, stranguria, and frequency. There were also reactions indicating a disturbance of the gastrointestinal tract; e.g., nausea, anorexia, heartburn, flatulence, cramps; and of the cardiovascular system; e.g., palpitation, tachycardia, flushes. Untoward effects upon skin and mucous membranes were excessive perspiration and dryness of nose and throat.

It is apparent that the majority of side effects are manifestations of the central nervous stimulatory action of Thephorin. This is in contrast to the depressant effect characteristic of Benadryl and Pyribenzamine. The wakefulness after Thephorin was overcome in many instances by the concomitant administration of a mild sedative. Clinically, the stimulant action of the new histamine antagonist reminds one of the effect of sympathomimetic drugs such as ephedrine and amphetamine. However, the latter substances are chemically unrelated to Thephorin and, devoid of antihistaminic properties, act in allergic patients chiefly as vasoconstrictors. Furthermore, even the prolonged use of Thephorin has generally no effect upon the patient's pulse rate, and an effect on the blood pressure was never observed.

In keeping with the drug's stimulatory action, fatigability was lessened in many patients. In one case of allergic rhinitis, Thephorin was discontinued because the patient took the drug also as a spur against mental and physical fatigue. When the medication was stopped, after 75 mg. had been administered daily for three months, there was no craving or any other complication attributable to the withdrawal of the drug. Incidentally, urinalyses, hemograms, and electrocardiographic tracings done for this patient at initiation, during, and at termination of treatment with Thephorin, showed no significant changes.

Another subject who had derived excellent relief from his hay fever asked for a further supply of Thephorin after the pollen season because of the drug's stimulant effect. His request was denied, and he too was not unduly disturbed when the medication was discontinued. While there was thus no indication of drug addiction, this possibility, no matter how remote, must be borne in mind as with any other stimulant.

As the study progressed, the incidence of side effects decreased due to greater care exercised in individualizing the dosage plan.

In children untoward reactions occurred more rarely than in adults. In only one of sixteen patients under the age of ten years were ill effects observed. This was a six-year-old boy who, on a daily dose of 75 mg., became slightly dizzy. The reaction abated upon reduction of dosage to 30 mg. a day. However, a six-year-old girl tolerated a daily dose of 75 mg. without any untoward reactions.

COMPARISON OF RESULTS WITH OTHER ANTIHISTAMINIC AGENTS

We have had no opportunity of rotating the patients routinely to Benadryl and Pyribenzamine after they had been treated with Thephorin. However, some of the subjects received the latter compound and one or both of the other two drugs at different times. Thus, Thephorin succeeded in five patients in whom both Benadryl and Pyribenzamine were ineffectual. Similarly, three subjects were benefited from Thephorin in whom either Benadryl or Pyribenzamine had failed. Conversely, three patients were not benefited from Thephorin, two of whom had responded satisfactorily to Pyribenzamine and one to Benadryl. Some subjects were helped by all three drugs, and others by none. However, the number of patients thus studied was too small to warrant a definite statement with regard to the comparative therapeutic value of these three histamine antagonists. It can be said, though, that, in general, smaller doses of Thephorin are required to produce salutary results than of the other two drugs.

COMMENT

It is evident from the observations made that Thephorin is a very effective agent in combatting allergic symptoms, although it produces a high incidence of side reactions. While these are rarely severe, it is advisable to initiate therapy with a small dose (25 to 50 mg. a day in the adult) and to increase this amount according to need, once the patient's tolerance is established. Thephorin offers an important advantage in that it hardly ever produces the sedation and drowsiness so commonly observed with the other antihistaminics.

SUMMARY AND CONCLUSIONS

A new histamine antagonist, 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate (Thephorin), was evaluated clinically in 140 allergic patients. Relief of symptoms was observed in 75 per cent. Best results were obtained in cases of nonseasonal and seasonal rhinitis. Over 80 per cent of these patients were helped, with almost 50 per cent of the total number of nasal allergies treated deriving excellent benefit. Similarly, in cases of seasonal asthma, Thephorin proved very effective. Other conditions included allergic conjunctivitis, urticaria, angioneurotic edema, neurodermatitis, contact dermatitis, and other miscellaneous allergic manifestations. The general trend of responses is discussed.

Side effects occurred in 39 per cent of the 140 subjects studied. However, even severe reactions, which were rarely encountered, required no measures other than discontinuation of the drug. The majority of side effects were manifestations of the stimulating effect of Thephorin. Insomnia may be prevented by the concomitant administration of a mild sedative-hypnotic. It is the lack of a depressant effect which distinguishes Thephorin from other antihistaminics.

(Continued on Page 416)

CLINICAL EXPERIENCES WITH ANTISTINE

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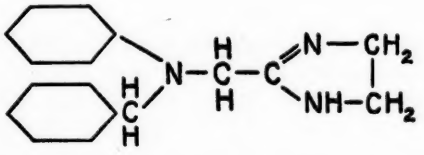
SINCE the development of the Fourneau and Rhone-Poulenc series of chemicals, great interest has been aroused in antihistaminic drugs. Chemists have succeeded in producing a number of such agents with varying degrees of antihistaminic activity. Needless to say, each compound put forward for clinical trial is tested for its ability to neutralize histamine *in vivo* and to prevent anaphylactic shock *in vivo*. In addition, the toxicity of each drug in clinical use must be determined, as some of these compounds possessing antihistaminic value have proven too toxic for use in humans. Recent studies summarized by Feinberg[2] have shown that two at least, Benadryl and Pyribenzamine, are clinically effective, but cause a high incidence of toxic side reactions.

In order to improve upon the records of the latter drugs, a new compound, 2-phenylbenzylaminomethyl-imidazoline (Antistine), was produced by Miescher in the laboratories of the Ciba Company in Basle. The product is related to Privine, 2-(naphthyl-[1']-methyl)-imidazoline hydrochloride. Its structural formula is:



Experimental work by Meier and Bucher[3] showed its effectiveness in the prevention of histamine effects in laboratory animals. Schindler[4] reported on its use in the treatment of asthma, urticaria, and pruritus. He claims that six of ten cases of asthma benefited from its use, ten of eleven cases of urticaria were helped, and nine of fifteen cases of pruritus of various etiology were helped. Bourquin[1] reported on its use in ophthalmology. He found response almost uniformly good in thirty-seven cases of various ocular disorders. Two patients complained of abdominal cramps and two of diarrhea. The only other side effect was pain and edema after accidental injection into the integument instead of the vein.

We have had the opportunity of using Antistine in a number of patients and feel that our results are worth reporting. A series of patients with various allergic complaints received Antistine for the control of symptoms, and the results are as follows:

Hay Fever.—To date, only two cases of tree pollen allergy have been treated. Both these patients were given Antistine tablets, 100 mg., as re-

quired, and obtained complete control of symptoms. Each complained particularly of conjunctivitis, and both were relieved satisfactorily by Antistine-Privine drops in the eyes. In addition to the above two cases, Antistine tablets have been used in several cases of preseasonal ragweed and grass hyposensitization for prevention and control of reactions. While such reactions have been few to date, Antistine would appear to be of value in allowing more freedom from reaction in this type of treatment. No drug reactions have been observed in these two cases.

Asthma.—Antistine was used in thirteen cases of asthma. Five of these are also cases of hay fever and all but two are of the extrinsic type. Five patients had good results when Antistine, 100 mg., was taken during attacks; four had some relief, not considered of much benefit, while four patients had no relief. Those who had good results had no side effects; one who had poor results had headache after taking the drug, and one had diarrhea. A young lady with severe perennial asthma, being treated by injections of autogenous vaccine, was given several injections of Antistine solution, 100 mg. each. At the site of two of the injections, considerable pain and induration developed, and a small area of necrosis eventually appeared at one site. However, she tolerated the drug orally in 50 mg. doses every three hours over a period of several weeks, without further side effects and with noticeable benefit.

Allergic Coryza.—Nine patients were given Antistine tablets and four were given Antistine nasal drops. These patients all had long-standing symptoms and were hypersensitive to several allergens. In only three were results noticeably good, while six did not respond. One of the latter was nauseated after taking the medication, and another had a gastrointestinal upset with cramps and diarrhea.

Urticaria.—Twelve cases of urticaria have been treated with Antistine, in eight of which the lesions were rapidly brought under control. One patient left off treatment, and three did not receive noticeable benefit. No side reactions occurred.

Eczema.—Antistine, 100 mg. every four hours, was given to five patients with severe eczema. In three cases no effect was observed. In the other two, excellent results were obtained, one patient stating that she was now able to perform many household tasks involving contact with dust, without having either eczema or asthma attacks, whereas she had formerly been assured of both if she was exposed to house dust. The other patient, who had developed conjunctivitis and blepharitis of the erythema type as a result of bacterial sensitization, was well controlled by Antistine tablets and drops in the eyes, though she experienced headaches after taking the tablets.

Contact Dermatitis.—Four patients were relieved of itching, and resolution of the lesions appeared to be hastened by the use of Antistine. No side effects were observed.

Pruritus.—Five cases of pruritus ani and one of varicose dermatitis were relieved of irritation by the use of Antistine. The drug was used in some orally; in all cases but one, a cream containing the drug in 2 per cent emulsion was also used. The pruritus associated with varicose dermatitis (one case) did not appear to benefit, while of the cases of pruritus ani treated, one patient was helped materially.

SUMMARY

In this report, the drug 2-phenylbenzylaminomethyl-imidazoline (Antistine) has been discussed and its use in a number of cases of allergic disorders has been described. As is the case with other antihistaminic drugs, Antistine appears to be most useful in the acute phases, and in those where the histamine mechanism is predominant in the causation of symptoms. It is less successful in chronic conditions (asthma, eczema) where other mechanisms play a greater part.

Side reactions have occurred in six of the series of forty-eight cases (12.5 per cent). Five of these reactions were related to the gastrointestinal tract, consisting chiefly of nausea, with three cases of more pronounced disturbance, including intestinal cramps and diarrhea; one headache was reported. No reaction was severe enough to require treatment other than withdrawal of medication. It is notable also that in four of the six cases with side effects, the clinical relief obtained was negligible. In the other two, reactions did not prevent the success of the treatment.

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REACTION: TETANUS ANTITOXIN

There is always danger that tetanus antitoxin may cause severe reactions in susceptible persons even if given in small doses for preventive purposes. Preliminary skin tests should be made to determine susceptibility to the antitoxin so that antitoxin can be given safely. Properly made skin tests do not cause general reaction. Whether drugs can be relied on to prevent anaphylactic reaction to tetanus antitoxin is not known. (J.A.M.A., Vol. 136, No. 17, p. 1118, April 24, 1948)

TREATMENT OF ALLERGIC AND OTHER DERMATOSES WITH PYRIBENZAMINE HYDROCHLORIDE

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IN 1945, Mayer, Huttner and Scholz[9] synthesized a number of pyridinoethylenediamines, the most promising of which was Pyribenzamine. Since then a number of studies have been made by Mayer and others on the antihistaminic, antianaphylactic and pharmacodynamic action of Pyribenzamine in experimental animals.

The remarkable capacity of this drug to nullify or compete with histamine in experimental sensitizations, together with its low toxicity, suggested its use in diseases in which the common denominator is the liberation of an excess of histamine.

Arbesman[2] and co-workers were the first to conduct clinical investigations. Their report included fifteen patients with acute urticaria, fourteen of whom were relieved with Pyribenzamine, and forty-four patients with chronic urticaria, thirty-three of whom were benefited. Three patients with cold urticaria were free from hives while taking the drug. Several patients with atopic dermatitis obtained rather decided relief from itching while taking Pyribenzamine. This group of 277 patients with various allergic disorders received from 100 to 400 mg. of Pyribenzamine daily, and only 5.4 per cent developed side effects.

Epstein[6] reported rapid and complete relief in eight patients with acute urticaria and symptomatic improvement in five of six cases with chronic urticaria. Pruritis was relieved in seven of nine cases of atopic dermatitis and in four of six with pruritus ani.

A summary of the literature[1,3,4,7,10,11] finds Pyribenzamine beneficial in the treatment of the following dermatoses: acute urticaria, 60 to 100 per cent; chronic urticaria, 60 to 83 per cent; atopic dermatitis, 9 to 100 per cent; contact dermatitis, 0 to 50 per cent; dermographism, 85 to 100 per cent; pruritus, either localized or associated with various dermatoses, 50 to 100 per cent. There is also mention of its value in hyperidrosis, dermatitis herpetiformis and in one patient with insect bites.

The following study of the effects of Pyribenzamine on dermatoses was begun in November, 1945, when Pyribenzamine was sent to us for clinical investigation. It covers 280 patients who were observed long enough to determine the value of Pyribenzamine. The standard oral dose was 50 mg. after meals and 100 mg. at bedtime for a minimum of one week unless symptoms disappeared or side effects developed.

From the Department of Dermatology, Columbia Presbyterian Medical Center, New York, N. Y.
N'-pyridyl-N'-benzyl-N-dimethylenediamine monohydrochloride (Pyribenzamine) was kindly furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J., until its acceptance by the Federal Drug Administration.

SERUM SICKNESS

Eight patients were admitted to the overnight ward with serum sickness due to tetanus or diphtheria antitoxin injections. All presented generalized urticaria, fever and intense pruritus. In three there was edema of the face, tongue and throat, and painful, swollen joints. Since these patients were under observation, 100 to 200 mg. of Pyribenzamine was given immediately. This was followed by 50 to 100 mg. every four hours for twenty-four hours. By this time, five were free from itching. The dose was reduced to 50 mg. after meals and 100 mg. at bedtime for four to five days. Within seventy-two hours, six of the patients were cured. The two remaining patients, both of whom had swollen joints, continued the medication for a week, by which time they were also free from all symptoms.

DERMOGRAPHISM

Four patients sought relief because of marked dermographism with pruritus. When the skin was stroked, a linear itching wheal soon appeared. Each took 50 mg. of Pyribenzamine after meals for one week. Following this, linear wheals appeared when the skin was stroked but there was no itching. Three of the patients, observed from one to five months, were free from itching and noted a diminution in the wheals on 50 mg. of Pyribenzamine after meals. The fourth patient who also had cholinergic urticaria took the standard dose for a month. At that time he was free from both symptoms. He was observed for four months, during which time there was no recurrence.

URTICARIA

Following Penicillin.—Eighteen patients, while undergoing penicillin therapy for an infectious disease, developed acute generalized urticaria. In twelve it was possible to discontinue penicillin and begin Pyribenzamine therapy within forty-eight hours of the onset of urticaria. From two to five days after Pyribenzamine was instituted, eleven were free from urticaria. One of these patients with several generalized hives of four days' duration, who had been receiving massive doses of penicillin for fulminating pulmonary coccidiosis, was entirely free from hives in thirty-six hours. The twelfth patient continued to have hives after seven days of Pyribenzamine therapy. The remaining six patients took Pyribenzamine along with the penicillin. None was free from hives, but itching was less severe. In five the Pyribenzamine was continued for a week after the penicillin injections were discontinued, and all were free from hives by this time. The sixth patient discontinued Pyribenzamine because of side effects.

Six additional patients with urticaria gave a history of having had injections of penicillin one to three months previously. No other cause for urticaria was found. After one to three weeks on Pyribenzamine, four

were free from hives. The remaining two discontinued it because of side effects.

Cold Urticaria.—In six patients, hives developed on exposure to cold. Three had just recovered from virus pneumonia. One patient noted that when he went out of doors in cold weather his skin began to tingle and swell. When he returned to a warm room, his face, arms and legs were quickly covered with hives, his tongue and lips became swollen and at times he had difficulty in swallowing. The attacks lasted from ten to eighteen days. On the sixth day of one of his attacks (March, 1946) he was admitted to the overnight ward. His face and tongue were markedly swollen, and his neck and upper extremities were covered with hives. He was given 150 mg. of Pyribenzamine immediately and 100 mg. after meals for twenty-four hours. The edema and itching disappeared in two hours and the wheals within twelve hours. This patient and the five others, with a similar history but less severe symptoms, were instructed to take 50 mg. of Pyribenzamine one-half hour before exposure to cold and to take an additional 50 mg. in half an hour if hives developed. During the winter months they were free from urticaria or the symptoms were minimal while varying the dose, depending on the weather and the length of exposure to it. When Pyribenzamine was not taken the symptoms recurred. In one patient, treatment could not be continued because of side effects.

Cholinergic Urticaria.—Three patients developed the characteristic small white hive after exposure to heat or when emotionally upset. As the provocative agents were rather unpredictable, these patients took 50 mg. of Pyribenzamine when they thought an attack imminent and again in an hour if unrelieved. Either the hives failed to appear or, if they did, itching was absent or minimal. One, a medical student, developed marked urticaria before each examination. On several occasions she has taken 50 mg. before an examination and had no urticaria. If she develops hives because of an unpredictable emotional strain, she takes 50 mg., and the hives do not itch, and disappear more rapidly than without the Pyribenzamine.

Food Urticaria.—Forty patients had a history of a specific food causing an attack, or subsequent study strongly suggested food as the cause. The duration was from two to twenty days. Eight patients, without any restriction in diet, were free from urticaria within three days on the standard dose of Pyribenzamine, and twelve had cleared within a week. There has been no recurrence over a period from one to eight months. One of these, a nurse, ate part of a dill pickle, and within a very short time developed swelling of the tongue and throat, difficulty in breathing and generalized hives with marked pruritus. Because of the severity of symptoms she was admitted to the hospital. Four years previously the patient had eaten a dill pickle. At that time she felt ill and had hives for a few days. The

patient received adrenaline, ephedrine and dihydroergotamine for forty-eight hours. Symptoms were unabated. The third day she was given 150 mg. of Pyribenzamine, and within two hours all symptoms had disappeared and she slept for fourteen hours. Pyribenzamine was continued for another day, a total of 350 mg., with no return of symptoms.

Fourteen patients continued to have urticaria after a week's trial of Pyribenzamine, but itching was absent or reduced. Six were not benefited. The drug was discontinued in three because of side effects.

Five patients ate the food to which they were sensitive an hour after taking 100 mg. of Pyribenzamine. Hives occurred in all, but itching was absent or minimal.

Due to Aspirin.—Two patients developed severe urticaria after aspirin. At one hour and at an hour and one-half, respectively, after taking 100 mg. of Pyribenzamine, they swallowed 5 grains of aspirin. One developed generalized giant hives in ten minutes and the other within thirty minutes. The patients felt that the attacks were as severe as previously, but in one the itching was less marked.

Due to Trichinosis.—One patient with trichinosis developed urticaria with severe itching. He received the standard dose of Pyribenzamine for one week. Itching was relieved within a few hours, and the hives disappeared in two days. On the tenth day the urticaria and itching recurred. The standard dose was again given for two weeks. The response was again prompt and there was no return of urticaria. The white blood cell count of around 5,000 with 15 to 20 per cent eosinophiles was not influenced by Pyribenzamine.

Of Unknown Cause.—Ninety patients, with chronic recurrent urticaria varying in duration from a few months to several years, were given the standard dose for at least two weeks unless side-effects developed. In five there was a complete disappearance of urticaria. Forty felt that the attacks of urticaria and particularly the itching were distinctly lessened while taking Pyribenzamine. One emotionally unstable patient had had recurrent giant hives for seven years. About once or twice a week it was impossible to go to work because of the marked swellings. On the standard dose she was free from attacks for two months. Then it was necessary to reduce the dose to 25 mg. twice daily because of dizziness. The patient has continued this dose for sixteen months. Mild swellings occur occasionally but are not incapacitating. Complete blood counts, done at monthly intervals, have remained normal. Thirty patients were not benefited, and fifteen discontinued the drug because of side effects.

ALLERGIC ECZEMA

Twenty adults with chronic recurrent eczema of the face, neck and flexures, who had been observed over a considerable period, were given

the standard dose of Pyribenzamine during an acute exacerbation. This supplemented an antiallergic regime and local medication. Twelve experienced appreciable relief from itching, were less irritable and slept better. Side effects were observed in four patients.

Twenty infants and children with generalized eczema and intractable itching were given from 10 to 30 mg. of Pyribenzamine at four-hour intervals for a few weeks. The incessant rubbing and scratching of the skin was greatly reduced in fifteen. Almost all slept from six to seven hours uninterruptedly at night with the Pyribenzamine. However, the eczema did not clear until the sensitizing allergens were removed from the diet and environment.

DERMATITIS VENENATA

Twenty-six patients had a dermatitis due to sensitization to substances with which they had come in contact. In ten it was due to poison ivy. These received the usual local treatment together with the standard dose of Pyribenzamine. Five who previously had had "poison ivy" felt that the outbreak and itching were less severe than previously. After the attack, two patients took the standard dose of Pyribenzamine for five days. On the third day a patch test to poison ivy (Lederle 1:5,000) was applied to the skin. A vesicular dermatitis appeared at the test site in twenty-four hours in both patients, but itching was absent.

The remaining sixteen patients had localized eruptions from one of the following substances: formaldehyde, hair dye, face powder, nail polish, nickel, zinc sulfate, mercury, nupercaine, penicillin, pyrethrum and primrose. They received the standard dose for a week. In ten the itching almost disappeared within a few days. In the remaining six, there was no change. Five discontinued the drug because of side effects.

PRURITUS

Generalized.—Five patients with intractable pruritus were given the standard dose for two weeks. Two were over eighty years of age, with wasted skin, and the remaining three were women in the latter half of pregnancy. All were relieved of itching as long as the drug was continued.

Localized.—Two patients with a marked pruritus of the legs from Nylon stocking were able to wear them if they took 25 to 50 mg. of Pyribenzamine three times a day.

Lichen Simplex Chronicus (Vidal).—Five patients with localized patches of eczema were given the standard dose of Pyribenzamine, and the areas were covered with a gauze bandage. The treatment was continued from three to four weeks. In four the itching subsided in a few days, and the patches cleared in about two weeks. In two the patches recurred after the Pyribenzamine was discontinued. One developed side effects.

Pruritus Ani.—Fifteen patients with marked itching of the anal area were given Pyribenzamine and an antipruritic ointment. After two to three weeks, ten were free from symptoms. A dose of 50 mg. after dinner and at bedtime was then given for another two weeks, with complete relief. The remaining five experienced little relief, and in three the drug was discontinued because of side effects.

OTHER ITCHING DERMATOSES

Four patients with severe erythema multiforme, in which wheals and itching were prominent symptoms, were given the standard dose for from four to fifteen days. One with a lymphosarcoma, who developed erythema multiforme after radiation, was free from itching and wheals in three days. The others noted a diminution in itching while on Pyribenzamine, but the lesions were not influenced. One with a history of dermatitis due to ragweed developed a severe dermatitis while receiving injections of ragweed antigen; another had a polymorphous generalized eruption after gold injections; two others had lichen planus of the extremities; a fifth had exudative discoid and chronic lichenoid dermatitis. All were given the standard dose of Pyribenzamine for at least a week in an attempt to allay the severe pruritus. In all the itching was suppressed or minimal and the skin less traumatized while on Pyribenzamine. Side effects developed in one patient.

SIDE EFFECTS

In thirty-six of the 280 patients, symptoms developed which caused them to stop Pyribenzamine. These usually occurred a few days after the drug was started. In none were the symptoms alarming, and in all they subsided shortly after the drug was discontinued. The nervous and gastrointestinal systems were most frequently affected. In order of frequency the patients expressed these symptoms as follows: feeling queer, drunk, dizzy, unsteady, nervous, hyperactive, drowsy, depressed, or developing headache, upset stomach, indigestion, dry mouth, vomiting, nausea, cramps, burning on urination, and palpitation.

COMMENT

The pioneer studies of Dale and Laidlaw[5] and of Lewis and Grant[8] demonstrated the similarity of allergic and anaphylactic reactions in man and animals to the effects produced by the injection of histamine.

Since then, numerous workers have attempted to inhibit these histamine effects. Recently the ethylenediamine derivatives, of which Pyribenzamine is one, have been developed. The unfolding of this research is well reviewed by Feinberg.[7]

Pyribenzamine is a most useful therapeutic agent in allergic symptoms which follow the administration of antitoxin or penicillin. Its continued use exerts a prophylactic action in patients with physical allergies and

dermographism. Lastly, it is most worthy of trial in a number of dermatoses in which itching is marked.

It is difficult to evaluate the efficacy of Pyribenzamine in a disease as elusive as urticaria. However, the promptness with which the urticaria disappeared in 25 per cent and was controlled in another 40 per cent while on Pyribenzamine warrants its use.

The results of Pyribenzamine therapy are summarized in Table I.

TABLE I. SUMMARY OF TREATMENT WITH PYRIBENZAMINE

Disease	Number of Patients	Results		Side-Effects
		Complete Relief	Suppressive Action	
Serum Sickness	8	6	2	0
Dermographism	4	1	3	0
Urticaria				
After penicillin	18	11	5	1
After penicillin (?)	6	4	0	2
Cold	6	0	5	1
Heat	3	0	3	0
Foods	40	20	14	3
Drugs	2	0	0	0
Parasites	1	0	1	0
Cause unknown	90	5	40	15
Allergic Eczema				
Infants	20	0	15	0
Adults	20	0	12	4
Dermatitis Venenata	26	0	15	5
Pruritus	27	0	21	4
Other Itching Dermatoses	9	0	8	1
Total	280	47	144	36

SUMMARY

Pyribenzamine was beneficial in the treatment of approximately 68 per cent (191 of 280) patients with allergic and other itching dermatoses.

Prompt and complete relief was obtained in patients with serum sickness and in many patients with urticaria due to penicillin.

The continued use of Pyribenzamine effectively controlled physical allergies and dermographism.

Pyribenzamine completely relieved or controlled the symptoms in 65 per cent of patients with urticaria and depressed itching in approximately 60 per cent of patients with allergic eczema, in 40 per cent with dermatitis venenata and in 75 per cent with pruritus.

The antipruritic and sedative effect of an orally administered drug makes Pyribenzamine a welcome adjuvant in the treatment of a variety of dermatoses accompanied by severe itching.

Pyribenzamine was discontinued in about 13 per cent of the patients because of side effects.

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BRONCHIAL ASTHMA DUE TO INGESTION OF FENNEL AND FENNEL SEED

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ALLERGY to fennel and fennel seed has been unreported in the literature.

Botanical History.—FENNEL[1] (AS. *fenol,* from Lat. *fœniculum,* fennel, diminutive of *fœnum, fœnum,* hay), *Fœniculum,* a genus of umbelliferous plants allied to dill, and[2] to carrot, celery, parsley and parsnip. The flowers are yellow. All the species are aromatic and have much divided leaves with threadlike segments. The best known is common fennel, *Fœniculum vulgare,* a native of the south of Europe. It is a biennial, 3 or 4 feet tall, cultivated in many gardens in both Europe and America, chiefly for the sake of its leaves, which are used for flavoring, but also for its aromatic seeds. Florence fennel, sweet fennel, Italian fennel, or Cretan fennel (*Fœniculum dulce*) is of lower growth, much cultivated in the south of Europe. The enlarged bases of its leafstalks, after being bleached like celery, are boiled and served with drawn butter like cauliflower. The fruit (seed) is longer and paler than that of common fennel, has a more agreeable odor and flavor, is the favorite aromatic condiment of the Italians, and is used in medicine. Oil of fennel, an aromatic, stimulant, and carminative essential oil, is also made from it. Cape fennel (*Fœniculum capense,* or *Carum capense*), found in the vicinity of the Cape of Good Hope, has a thick, aromatic esculent root. The Panmuhoree of India (*Fœniculum panmorium*) is a species of fennel much cultivated in its native country for its sweet, warm, and aromatic fruit, which is much used as a carminative and in curries. The "giant fennel" of the south of Europe is a plant of a different genus (*Ferula*) and abounds in a fetid juice. It is, indeed, closely allied to asafetida. The species mentioned above, except *Fœniculum capense,* have recently been combined under the name *Fœniculum vulgare.*

CASE REPORT

A nine-year-old boy (J. P.) of Italian descent, complaining of seasonal hay fever and asthma of two years' duration, was first seen on October 29, 1946. Family history: A paternal uncle had asthma. Past history: The patient had the usual childhood diseases, and had a tonsillectomy and adenoidectomy at five years of age because of frequent "colds."

Present illness: The patient had been well until August and September, 1945, when he developed his first seasonal hay fever. Early in November, 1945, he had a two-day attack of asthma which required adrenaline for relief. He remained well until August and September, 1946, when hay fever recurred. During October, 1946, there were many attacks of asthma, several of them severe enough to require repeated injections of epinephrine. The boy's parents stated that some of the asthmatic at-

tacks occurred within five minutes after eating fennel and sausages containing fennel seed.

Physical examination revealed a well-developed and well-nourished boy with marked dyspnea, wheeze, and cough. The chest was hyperresonant to percussion, and the lungs were filled with sibilant and sonorous râles more on expiration than inspiration. The breath sounds were distant. Epinephrine 0.3 c.c. relieved the attack, and twenty-four hours later the chest and lungs were normal.

Intradermal skin tests demonstrated positive reactions to ragweed pollen, fennel, and fennel seed. Passive transfer tests, using the father as the recipient, were positive for ragweed, fennel and fennel seed; these reactions were marked, and the reaction for the fennel test was accompanied by intense itching.

Asthmatic attacks were reproduced several times by eating fennel and sausages containing fennel seed; sausages without fennel seed did not cause asthma. The patient was placed on perennial ragweed therapy, and fennel and fennel seed were eliminated from his diet. He has been completely free of asthma since the omission of these foods.

SUMMARY

1. Bronchial asthma due to ingestion of fennel and fennel seed is here reported for the first time.

2. Positive skin tests with these allergens, the transfer of their reagins passively to a recipient, the reproduction of asthma after eating these foods, and the relief from asthma by their elimination from the diet, demonstrate that fennel and fennel seed may be a cause of bronchial asthma.

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STUDY OF A NEW HISTAMINE ANTAGONIST

(Continued from Page 404)

The new compound provides only symptomatic relief, as do the other histamine antagonists established in therapeutics. These preparations are no substitutes for the usual procedures in the therapy of allergy, such as elimination of allergens and hyposensitization. Thephorin was found to be a valuable adjuvant to such treatment. It also proved effective in relieving allergic symptoms in a great precentage of patients not undergoing the usual procedures.

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NONREAGINIC ALLERGY

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THE approach to allergic problems has had many varied routes. Recently the psychosomatic approach is enjoying its heyday, and perhaps justifiably so. If, however, we are content to utilize only the psychogenic equilibrium of the individual as a means to a cure, it is my personal opinion that we are, in reality, then assuming that allergy *per se* does not exist. The greatest deterrent, therefore, to the writing of this paper is the possible criticism that this diagnostic method is also a devious channel to a substitution phenomenon on the patient's part.

We, as allergists, are accepting many unusual and previously unclassified syndromes and illnesses as having an allergic insult as their etiological factor. Coca,[1] several years ago, advanced the opinion that nonreaginic allergy is responsible for many of the unusual patient problems. After two years' study and application of this theory, I believe an attempt at confirmation of his original ideation is indicated.

My enthusiasm for this approach stems from the fact that cutaneous reactions, especially in food sensitivity, fail in such a high percentage of cases that they are valueless. Elimination diets are, of necessity, so discouraging to the patient in the time element involved, that it is difficult to complete a case unless one is unusually lucky in hitting the offending food early. They also fail to take into account that any one food may be the offender and that its ability to consistently provoke an allergic insult is lacking. This latter statement, I am sure, will find agreement among all allergists.

The explanation as to why the cardiovascular apparatus is invariably sensitized is very difficult physiologically. Possibly it is still due to the response of the vascular system to a histamine-like substance, although most opinions are to the contrary. In the same line of reasoning, it is peculiar that, at least in my experience, none of the antihistaminic drugs suppress the allergic reaction or the acceleration of the pulse. Peculiarly, however, histamine given either in fractional daily doses or intravenously does alter the pulse response and does control the symptoms. This is graphically illustrated in Figures 1 and 2.

Figure 1 shows the effect of fractional daily doses, while Figure 2 shows the effect of intravenous histamine in the dosage indicated; it is of interest that this patient, after three months, is still symptom free, although cereal and egg have both been reintroduced into his diet.

Coca has presented good evidence that severance of the sympathetic chain will also alter the pulse response but that it will not consistently remove either the symptomatology or the acceleration phenomenon to all the allergens. It is, therefore, still a confusing issue from a physiologic, pharmacologic basis.

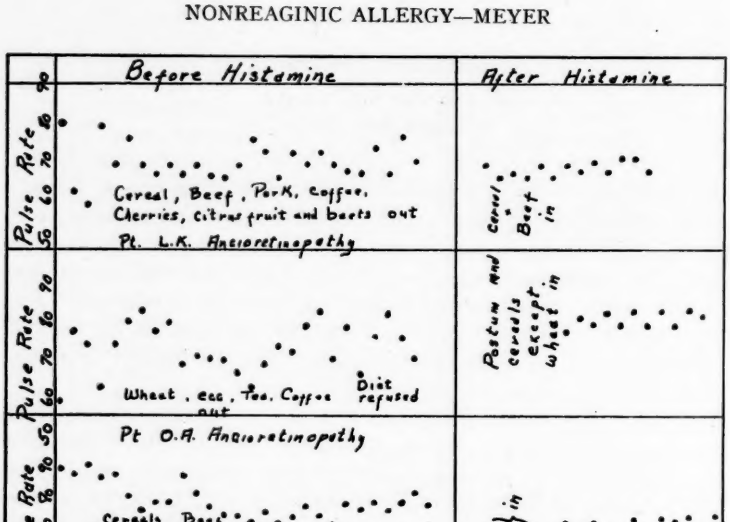

Fig. 1.

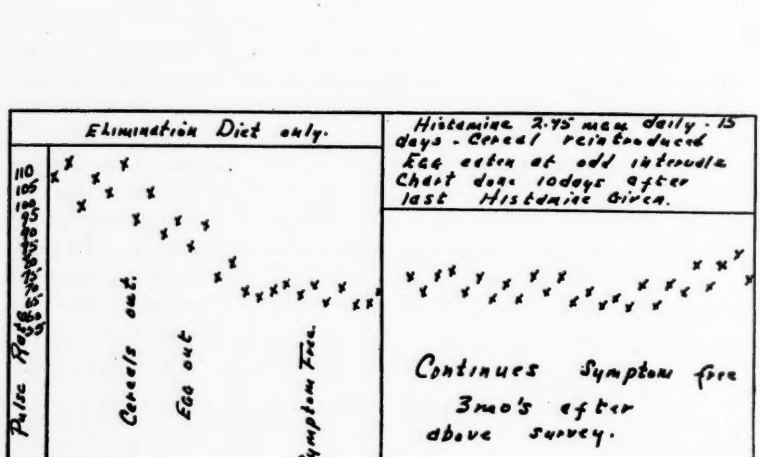

Fig. 2. F.B., aged forty-seven. Gastric ulcer. X-ray and gastroscopic proof. Two-year history. Operation refused.

The method of survey which I have used differs from that employed by Dr. Coca in this respect. I find it difficult to limit the patient accurately to one food per day or one food per meal. As a consequence, I start them off with the following directions:

"The following instructions are given for your convenience in attempting to find the foods to which you are sensitive. It has been shown that most illnesses which are not caused by infections are generally the result of sensitivity to food or contacts.

"It must be clearly understood that unless these instructions are followed in exact detail, you are wasting your time as well as mine.

"The importance of accurately counting the pulse cannot be overemphasized. The valuation of a few points may alter the accuracy of the test since the whole principle of this procedure depends on accurate records. Proceed as follows:

"1. On the day before the test diet is started, eat nothing following the noon meal, and count the pulse at 4:00 p. m., 8:00 p. m., and 9:00 p. m. Instructions for counting pulse are on the reverse side.

"2. Count the pulse on awakening before getting out of bed.

"3. Count the pulse just before each meal.

"4. Count the pulse one-half hour, one hour, and one and one-half hours after each meal. Always sit down and rest for two minutes before taking pulse.

"5. On the first two days of the diet eat the menu on the accompanying chart exactly. Do not add any articles to it until you have either phoned me the pulse readings or given them to me in person. Salt may be used as desired.

"6. Prepare all foods in either glassware or enamelware rather than aluminum.

"7. Keep the chart as indicated on the accompanying sheet.

"8. List all symptoms noted, such as headache, indigestion, excessive gas, joint pains, diarrhea, vomiting, heart consciousness, constipation, et cetera."

These instructions may seem rather dramatic in their presentation to the patient, but drama appeals more to the average person than simple statement of fact and they are more apt to co-operate fully. I will delete the use of enamelware rather than aluminum on my next set of instructions since I, personally, have failed to find instances of aluminum sensitivity. Dr. Coca shows evidence that it exists. The importance of physical and mental rest during the pulse-counting interval must be impressed. Whether or not one is wrong in having the patient count his own pulse, I do not know. Certainly, hospitalization for the average individual, without complete necessity for daily observation, is hardly indicated in these times. I must also say that I am very hesitant to put all suspected allergic patients on this survey, because in some instances I have sensitized them to their radial pulse to a much greater degree than to food or contact. If the patient's symptoms are severe enough, they will co-operate well. If they are only of a mild to moderate annoyance, they will not subject themselves to the details involved. If the decision to utilize this method has been made, the following diet is given for two successive days:

Pulse rate 4:00 p. m. Day before test starts	8:00 p. m.	Before arising 9:00 p. m. Day of test
Menu	*Pulse Rates*	*Symptoms*
Rice Milk Sugar Grapefruit	Before ½ hr. after 1 hr. after 1½ hr. after	
Beef Peas Potatoes Lettuce (No dressing) Pears (Water packed) or Fresh Apple	Before ½ hr. after 1 hr. after 1½ hr. after	
Rice Sugar Milk Butter Cheese	Before ½ hr. after 1 hr. after 1½ hr. after	
Second Day		*Pulse before arising*
Whole wheat bread Milk Butter Egg	Before ½ hr. after 1 hr. after 1½ hr. after	
Beef Carrots Lettuce Beets	Before ½ hr. after 1 hr. after 1½ hr. after	
Whole wheat bread Peas Chicken Grapefruit	Before ½ hr. after 1 hr. after 1½ hr. after	

I do not believe it is any better and probably not as good as other individuals will work out for themselves. I have accustomed myself to interpret it, and for that reason use it. My line of reasoning in this diet is as follows: The breakfast on this first day is aimed primarily at milk and citrus fruit. If the former, there is a chance for a recheck at supper of the same day, and if the latter, a recheck for supper of the second day. Rice and sugar, in my experience, are uncommon allergens. I have one patient sensitized to cane sugar and not to beet sugar, and only four who are sensitized to all cereals, including rice. Dinner of the first day eliminates

cereal and milk, and if a pulse response occurs here, an opportunity for a recheck on peas, a fairly common allergen, is given at the second dinner. If beef or potatoes seem indicated, a recheck at the second supper is possible, provided citrus fruit has not been incriminatory. The first day's

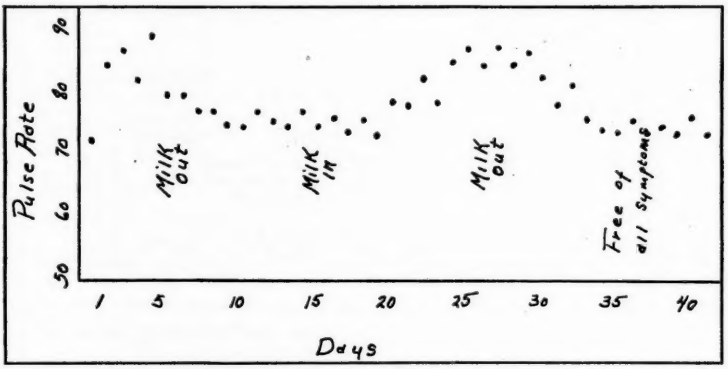

Fig. 3. C. S., aged forty. Clinical peptic ulcer. X-ray proof.

supper is obviously pointed at dairy products, and if the patient is sensitized to the same, a marked pulse response is almost always obtained here. Breakfast of the second day introduces both egg and wheat, very common allergens. Opportunity for a recheck of wheat has been given on the previous day and is repeated at the second day's supper. The second dinner eliminates potatoes, occasionally encountered, and gives an opportunity to check a delayed reaction to beef since carrots and lettuce are also uncommon allergens. The supper of the second day introduces fowl, which is easily spotted if no previous tachycardia has been registered. Since dairy products, wheat, egg and citrus fruit are, in my opinion, the most common of food allergens, my primary interest in these two days centers on these foods. Obviously, from this point on, addition or substraction of foods, introducing one new one per day, allows us to continue the survey intelligently.

The application of this method should not be attempted unless one has thoroughly acquainted himself with the chapters of Coca's book indicating the difficulties of interpretation. They exist to such an extent that I have had to abandon many patients simply because I could not identify the pulse accelerator. These difficulties are briefly reviewed. Figure 3 indicates the latent period of temporary loss of sensitivity. It will be noted that after primary elimination of milk, with its reintroduction there are four days before a pulse acceleration occurs, and that the resultant tachycardia persists for forty-eight hours after milk is eliminated, the latter being known as the carry-over reaction.

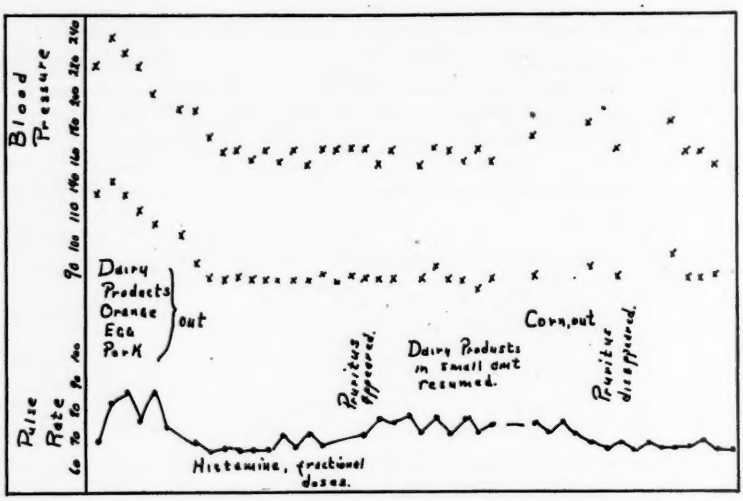

Fig. 4. F. M., aged sixty. Hypertension was relieved, then followed by pruritus, which was relieved.

Figure 4 shows the importance of major and minor allergens. This patient first experienced dramatic relief following the removal of the primary allergen, only to have a new allergic symptom manifest itself later. Removal of corn then cleared the pruritus. This may indicate the specificity of allergens.

The sensitivity to a large number of foods, or at least a continuous pulse elevation, is seen quite often. Care must be taken to rule out the effects of known or unknown inhalants or contacts. The latter is shown graphically in Figure 5. It is readily seen that the hypertension and the relative tachycardia were controlled perfectly while these patients were ambulatory in the hospital, and with the same degree of activity were not controlled on return home.

The specificity of allergens is an interesting phenomenon, and another illustrative example is given in Figure 6. The elimination of dairy products relieved the arthralgia. The elimination of wool contacts relieved the asthma, and although a tachycardia to potatoes persists, no symptoms were gained from their use. This patient, however, was operated upon for endometriosis one month ago, but I refuse to draw conclusions from that.

It is worth repeating that not all patients are candidates for this type of survey. I consider the following factors:

Is the patient of a relatively stable personality, without too much evidence of vasomotor instability?

Is he willing to forego his pleasure in food ingestion to follow this program carefully?

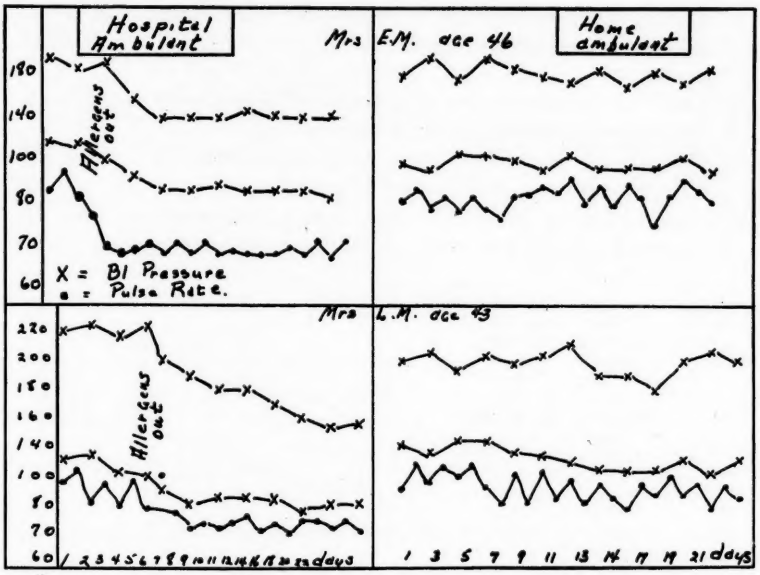

Fig. 5.

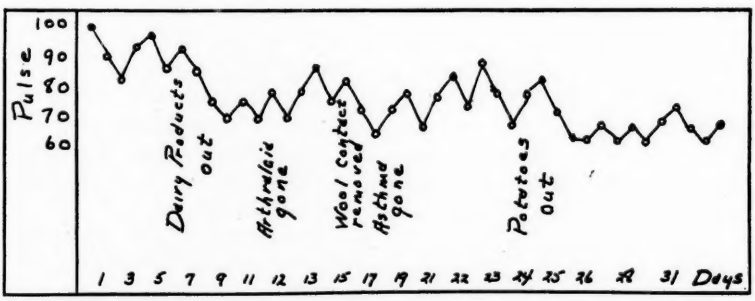

Fig. 6. C. K., aged thirty-eight. Arthralgia, asthma. After three weeks of eliminating potatoes, patient is reingesting them since she has no subjective symptoms from eating them.

Is his patience sufficient to give the allergist several weeks of a carefully followed routine?

Is he intelligent enough to realize that the analysis does not always result in success?

If the problem is solved, is he of the type that would be willing to continue on a restricted program?

That these patients represented cures based on allergen removal is considered only if the following axioms are met:

1. That there is a personal and familial history of a similar situation or an illness for which no definite etiological factor has been previously attributed.
2. That these symptoms have disappeared and reappeared as the foods involved were eliminated and reingested.
3. That with the ingestion of these foods, an accelerated pulse is manifest if extraneous conditions are controlled.

The total number of patients in whom a successful result was obtained by the methods previously outlined are shown in the following review:

Irritable Colon Syndrome	20
Peptic Ulcer	2
Ulcerative Colitis	1
Migraine	13
Ménière's Disease	6
Chronic Rhinitis	4
Retinal Angiopathies	3
Urticaria	7
Epileptiform Seizures	5
Paroxysmal Tachycardia	5
Angina Pectoris (with EKG changes)	3
Chronic Asthmatic Bronchitis	4
Emotional Instability and Depressions	8
*Multiple Sclerosis	2
Hypertension	24
Myalgias	3
Pruritus Ani and Vulvae	6
Total	116

Hypertension presents a challenge. It continues to lead the parade as a cause of death in the United States. Certainly any procedure which not only reduces the pressure but seemingly prevents the complications which give an untimely end to these people is worth a trial. The total number of hypertensives attempted on this management is forty. Control in twenty-four represents an incidence of 60 per cent. This compares favorably with the rice and fruit juice diet, which may represent exactly the same method of treatment. Control is regarded if the diastolic pressure is below 100 after it has consistently been above 100 prior to elimination therapy. The average diastolic pressure of those treated is now 86. Table I shows six typical examples of patients who have been followed longer than eighteen months and who continue to be well controlled, and in whom, as in the other eighteen, no complications involving progressive renal or cardiac damage have been noted.

Although it is generally agreed that when renal damage exists to a degree recognizable by laboratory procedures, little can be offered, I should like to mention two patients who have had both clinical and laboratory improvement following elimination therapy. This is shown in Table II.

*Multiple sclerosis is a long and unpredictable illness. The patients mentioned have had a remission for better than fifteen months, but conclusions cannot be drawn from that at this time. Diabetes mellitus was originally placed on this chart and then removed. Three mild cases have been controlled for over a year without insulin and with the elimination of foods that were not necessarily high in carbohydrate value. However, any diabetic, knowing that he has the illness, is very apt to eliminate foods excessively high in carbohydrates as a matter of precaution.

TABLE I

Name	Age	Previous Blood Pressure (6 or More Readings, Avg.)	Present Blood Pressure (10 or More Readings, Avg.)	Allergens	No. of Months Followed
Mrs. P.M.	52	190-S 110-D	140-S 86-D	Beef, peas, str. beans, tomatoes, spinach	22
Mrs. S.R.	64	220-S 130-D	160-S 90-D	Eggs, celery, citrus fruit, apples	21
Mrs. M.M.	58	190-S 110-D	150-S 84-D	Potatoes, beef, peas, str. beans	21
E.P.	40	166-S 100-D	142-S 84-D	Citrus fruit, cane sugar, fish	21
Mrs. J.F.	47	180-S 120-D	146-S 80-D	Eggs, pork, coffee, choc., chicken	21
J.D.	38	158-S 100-D	130-S 76-D	Chocolate	21

TABLE II

Name	Before Allergens Out			After Allergens Out		
	B.P.	Urine	Chemistry	B.P.	Urine	Chemistry
Mrs. E. L. Age 36 Dizziness Headache Exertional Dyspnea Heart conscious	250/140 230/136	Sp. Gr. 1.004 Alb.-Tr. Micro. 3-4 Hyaline 1-2 granular HPF	NPN-48 Urea N.-30 PSP 1 Hr.-20% 2 Hr.-22%	160/88 158/84 158/82	Sp. Gr. 1.016 Alb.-0 Micro. Amorph. urates only Only occasional headache now	NPN-32 Urea N.-18 PSP 1 Hr.-40% 2 Hr.-16%
Mrs. S. R. Age 62 "Palsy" Dizziness Exertional palpitation Angina Dyspnea	210/130 220/134 –	Sp. Gr. 1.006 Alb.-+ Micro. 7-8 Hyaline 4-5 granular HPF	NPN-52 Urea N.-32 PSP 1 Hr.-28 2 Hr.-18	170/90 172/88 168/88	Sp. Gr. 1.014 Alb.-spt. Micro. 1-2 Hyaline HPF Dyspnea only-T with marked exertion	NPN-40 Urea N.-20 PSP 1 Hr.-40 2 Hr.-20

TABLE III

Name	Age	Average Frequency of Attacks	Grand Mal	Frequency	Medication As Before
B. B.	24	3 times weekly	+	3 times weekly	+
L. C.	19	5 times yearly	+	2 times in 15 mos.	+
L. N.	34	2 times monthly	+	1 time in 4 mos. known diet indiscretion	0
M. M.	62	2 times monthly	+	1 time in 6 mos.	0
C. T.	64	3 times weekly	+	2 times in 10 mos.	½ dosage Dilantin S.
L. S.	26	3 times daily	0	3 times daily	+
E. P.	58	4 times monthly	0	1 time in 6 weeks	No medication

Gastrointestinal complaints, when functional, I believe, are all of allergic origin. I admit the etiological factor of nervous tension but, as in all allergies, I believe that the trigger mechanism would not be effective if the

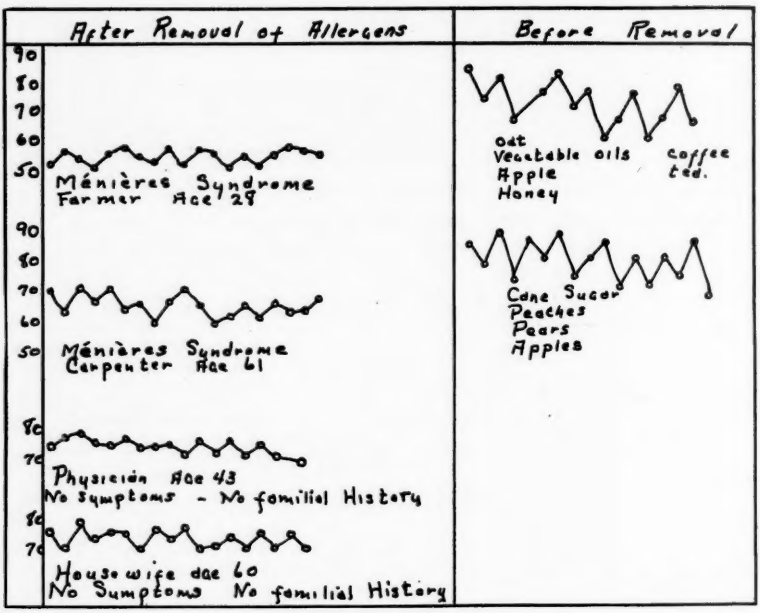

Fig. 7.

individual were not of an allergic diathesis. Certainly all high-tension individuals do not have a bellyache.

Twenty-five successive cases with gastrointestinal complaints were studied by our group. Of these twenty-five, nine showed clinical and x-ray evidence of organic disease, such as cholelithiasis, peptic ulcer and malignancies. Of the remaining sixteen, fifteen are completely free of symptoms following the removal of foods which caused a relative tachycardia. In addition, two patients with peptic ulcer, proven radiologically, have had both subjective and objective cure by the elimination of offending foods.

That the nervous system is often the shock tissue is an accepted fact. Experience with epileptiform seizures are shown in Table III. These are not good results but do indicate some specificity. At least in most of them, the medication has been reduced and the number of attacks have been greatly lessened.

Ménière's Syndrome and its relief are illustrated in Figure 7. This is also shown as an indication of how well pulse stability is attained in the individuals after elimination of foods has been accomplished, and how relatively stable the pulse is in two individuals in whom no symptoms appeared which might possibly be interpreted as allergic.

A rather large number of migraines have been well controlled. A typical migraine case is as follows:

Mrs. E. B., aged thirty-seven, with a typical unilateral headache associated with visual disturbances, occurring two to four times monthly, was seen with an entrance complaint of pruritus vulvae. The headaches were regarded by this patient as incurable and were not mentioned in the original complaints. After the elimination of milk, she volunteered the information that she had had migraine which has disappeared entirely. The pruritus, in turn, had not disappeared, and it was only after energetic treatment for the trichomonas infection by another member of our group that the pruritus disappeared.

Cephalalgias not necessarily of a migraine type are also worth investigation, as illustrated by the following case report:

D. B., aged twenty-two, has had severe headaches following his discharge from the army, where he had had a rather severe cerebral concussion following a land mine explosion. Complete neurological examination and spinal fluid examination were negative for pathologic conditions. This patient, however, showed a pulse rate rising from 64 to 110 every time eggs in any form were ingested. After the elimination of eggs on October 10, 1947, he has had no headaches and is working as a laborer in a construction company.

Peculiar myalgias and arthralgias failing to fit any category are often seen. An eosinophilia is suspicious. The sedimentation rate may be normal or elevated. A low grade fever is possible. Cardiographic evidence of rheumatic heart disease is lacking. The patients are chronically and painfully disabled. They are worth a trial. A previous chart showed disappearance of arthralgia in an individual following the elimination of dairy products. Another case history represents rather a dramatic cure:

S. H., aged nineteen, had been hospitalized elsewhere for over four months with arthralgia and myalgia. She had a sedimentation rate of 14 to 20 and a persistent eosinophilia of 6 to 8 per cent. Numerous muscle biopsies were negative for trichinosis. One consultant had suggested allergy, and histamine in large doses had been given, with rather dramatic relief when given two to three times daily. Two weeks of study revealed a pulse acceleration to walnuts, pork and egg. Within seventy-two hours following the removal of these allergens, symptoms subsided. The young lady has returned to school, is taking part in her class play and is planning to continue her studies as a physical education major.

In conclusion, then, my personal opinion is that this pulse dietary method of diagnosis is a distinct weapon in the armamentarium of allergists. However, it is not the answer. It is too time-consuming for both physician and patient. It is too difficult for the average patient to eliminate common foods, which unfortunately seem to be the most common allergens. I have indicated that intravenous histamine may be the answer. Yet, it too is not simple enough for the average patient. Antihistaminics are not the answer to date, and severance of the sympathetic chain is too hazardous an approach to the problem for the average patient.

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CONTROL OF ALLERGY TO ANTIRABIC VACCINE

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SINCE the institution of vaccine therapy for the protection against rabies, numerous reactions have been reported due to the vaccine used. These reactions have ranged from the simple swelling at the site of the injections to the dangerous neurological symptoms of ascending paralysis and involvement of the brain, with death.

At the first rabies conference of the League of Nations, Remlinger[8] reported an incidence of severe reactions to the Pasteur treatment of 329 in 1,164,264 treated victims of dog bite. McKendrick,[6] since that time, also reported thirty-three cases in 175,000 people treated. The incidence of severe reactions reported by numerous state health departments averages about 0.083 per cent with mortality between 10 per cent and 16 per cent. These statistics reveal the seriousness of the situation prevalent today.

Many theories have been advanced to explain these reactions. The controversy regarding the etiology of the paralysis has been present since the institution of vaccine prophylaxis. Babes[1] expounded the theory that the reaction was due to the rabies toxin and its predilection for nerve tissue. Koch[5] believed the paralysis was due to the canine rabies and not the vaccine. Many investigators were of the opinion that the reaction was due to a fixed virus. Prausnitz[7] believed that the reaction was due to the injection of heterogenous nerve substance in especially predisposed susceptible people. In 1918, Cornwall[3] concluded that the reactions were allergic in nature, resulting from the injection of foreign nerve substance (protein). Schwenther and Rivers,[9] in 1934, discovered that brain tissue under proper conditions functions as a complete antigen, and is capable of exciting in rabbits the development of complement-fixating antibodies, which are organ-specific rather than species-specific. In 1936, Burky and Henton[2] found that repeated injections of lens extract plus staphylococcus toxin gave rise to a skin sensitivity to lens extract, and that if the lens of a sensitized animal was injured by needling, there developed an intraocular inflammation which clinically and histiologically resembled endophthalmitis phaco-anaphylactica. This inflammation was believed to be due to the absorption of lens protein by the hypersensitive subject. They devised a method of desensitization, using the lens extract and staphylococcus toxin. The eye improved as the animal lost skin sensitivity. This showed that a reduction of skin sensitivity also produced a reduction in organ complement-fixing antibody reaction.

In 1939, Horak[4] reviewed the literature carefully and presented many cases of rabies vaccine reaction. He revealed that an allergic reaction was present in 87.5 per cent of the paralytic cases, and in 33 per cent of those cases which did not develop neurological symptoms. He also classified the

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reactions into six groups and advised gradual desensitization to the vaccine to prevent the allergic skin reaction. He reasoned that the prevention of the skin allergy would prevent the neurological sequellae which can prove fatal. Because his classification is so all-inclusive, it bears repetition:

Group 1.—Cases which develop a generalized urticarial rash, which respond to epinephrine promptly. There is no mortality in this group, and a history of previous injections may be obtained.

Group 2.—Delayed reactions of the tuberculin type, which occur at the site of the injections. These are most common and are not serious.

Group 3.—Reactions similar to Group 2, but much more severe and frequently associated with fever, headache, nausea and generalized adenopathy. Each injection is apt to cause redness at site of previous injection. This group is prone to develop paralysis, and caution should be used.

Group 4.—Simple neuritis involving the peripheral and cranial nerves, the facial nerve being the most commonly involved. The paralysis is usually transitory.

Group 5.—Dorsal lumbar myelitis most often occurring during the second and third weeks of treatment, and characterized by the gradual onset of fever, weakness, and terminating in paralysis, particularly of the lower extremities. There is also numbness and tingling of the lower extremities and sphincter disturbances preceding the paralysis. Local reactions of Group 3 are frequently present. The mortality rate is low in this group.

Group 6.—Paralysis of the Landry type—sudden in onset, often with high fever, nausea and headache, girdle pains, retention of urine, insomnia, and ascending paralysis. In one-third of the cases, bulbar paralysis ensues and death occurs. The local reactions are of Group 3.

Thomas,[10] in 1944, also reviewed the literature and presented a case of paralysis, following antirabic vaccine therapy which apparently responded to large doses of vitamin B_1.

In view of the evidence pointing towards the allergic etiology of these vaccine reactions, it was decided to attempt inhibition of the skin reactions by the use of the recently proven antihistamine drug, Benadryl. Since it is possible to prevent generalized organ-specific reactions in sensitized subjects by desensitization of the skin, the use of such a drug to prevent skin reactivity and generalized allergic reactivity seemed logical. In the following case report, the drug undoubtedly suppressed the allergic reaction to the vaccine used.

CASE REPORT

On May 3, 1947, Dr. Elmer Amerman, a pediatrician, referred a ten-year-old boy, A. T., Jr., for antirabic vaccine prophylaxis. The possibility of an allergic reaction presented itself because of a positive family history, so that extreme caution had to be exercised while giving the inoculations. This boy had sustained a rat bite to

his right index finger five days previously. The wound had been cleansed and washed, and a local physician had injected 300,000 units of penicillin (Romansky formula) intramuscularly, on the same day and on the following day.

Because of the prevalence of endemic rabies in wild rats, it was deemed essential that the patient be given prophylactic antirabic therapy. Lederle's Semple vaccine was obtained, and the first injection of 2 c.c. was given under the skin into the interscapular region. After the second daily injection the boy developed severe generalized urticaria. Benadryl was instituted in the dose of 50 mg. three times daily. This produced some drowsiness but completely controlled the generalized urticaria. The following injections were easily tolerated during Benadryl therapy. After the fifth injection, the patient stopped the drug voluntarily, and then developed a marked flare-up at each injection site with headache, nausea and slight fever. The drug was immediately resumed and 100 mg. caused the reaction to subside almost completely. The remaining injections were given, and no neurological symptoms developed. The Benadryl was continued for several days and then stopped. No further allergic reaction was manifest up to this time.

In order to prove that the reaction was not due to the previous penicillin used, a repeat test was done which did not elicit any allergic response. A repeat test of Semple vaccine, however, reproduced a flare of the previous injection sites, proving that the vaccine was the only offender.

COMMENT

According to Horak's classification, this case belongs to Group 3, in which neurological complications can frequently follow. There is no doubt that Benadryl inhibited the skin allergy and so probably prevented more serious sequellae. If this can be accomplished with such simple medication, the use of skin desensitization seems cumbersome and time-consuming. Whether this method of preventing the skin reactions is completely efficacious in preventing the neurological complications, remains to be proven by further study of thousands of cases.

CONCLUSION

Benadryl can inhibit the skin reactions to antirabic vaccine.

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A FALL-POLLINATING RED BERRY JUNIPER

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PREVIOUSLY recognized cedar hay fever in the Southwest usually begins about mid or late December and lasts until late February. It is caused by pollen from *Juniperus ashei*—sometimes referred to as *J. Sabinoides, J. Mexicana,* or *J. tetragona.* The common name of "mountain cedar" is often applied, but it is not a species confined to the mountains, and thus this is a misnomer.

The purpose of this paper is to describe a type of cedar not hitherto known to produce hay fever. As early as 1933, Hulsey[4] reported cedar pollen in Fort Worth, Texas, in November. Sellers,[10] farther west in Abilene, noted cedar pollen in the air in the latter part of September. Apparently, however, no one knew the exact origin of this pollen. It did not occur in very large amounts, although Sellers found significant quantities of it, and he felt that it was producing definite symptoms in his cedar-sensitive patients. In pollen counts for ten years in Abilene, he reported high cedar counts in October, diminishing in November, almost disappearing in early December, and again reaching high peaks in the latter part of December, continuing through January and part of February. Thus, there seemed to be two separate cedar seasons, as indeed there are.

In 1937 we first discovered that there was a cedar which pollinated in the months of October and November. It was called to our attention by patients living in southwest Texas who had hay fever at that time, and they definitely were able to associate their symptoms with this period of cedar pollination. Following this observation, we have encountered other patients who have hay fever due to this cedar.

Subsequently, in 1946, Mr. T. R. Stemen[11] identified this as a distinct species of cedar which was originally described by Sudworth[12] in 1905. It was called by him *Juniperus Pinchoti* in honor of Mr. Gifford Pinchot who at that time was professor of forestry at Yale, and later became governor of Pennsylvania.

In seeking further information about this species of cedar, we found that Mr. S. E. Wolff,[13] U. S. Department of Agriculture, had been making a study of it for many years. The map, showing its distribution in more than sixty counties of Texas (Fig. 1), and the following botanical description (Fig. 2) were compiled by him:

Habit.—An open spreading shrub, with several semi-prostrate (nearly upright in good sites on the eastern side of its range) stems 3 to 12 feet or even 18 feet tall, with a maximum diameter of 8 inches. No central stem develops. The stems at the groundline develop a prominent bud zone, or stem collar. This shows up early in the life of the seedling as a ring of buds. As the stems increase in diameter and

From the Department of Allergy, Scott and White Clinic, Temple, Texas.

more wood forms more buds are initiated until a bulge as large as a man's head may develop. Sprouts from this collar or bulge elongate whenever some or all the old stems are cut or burned off.

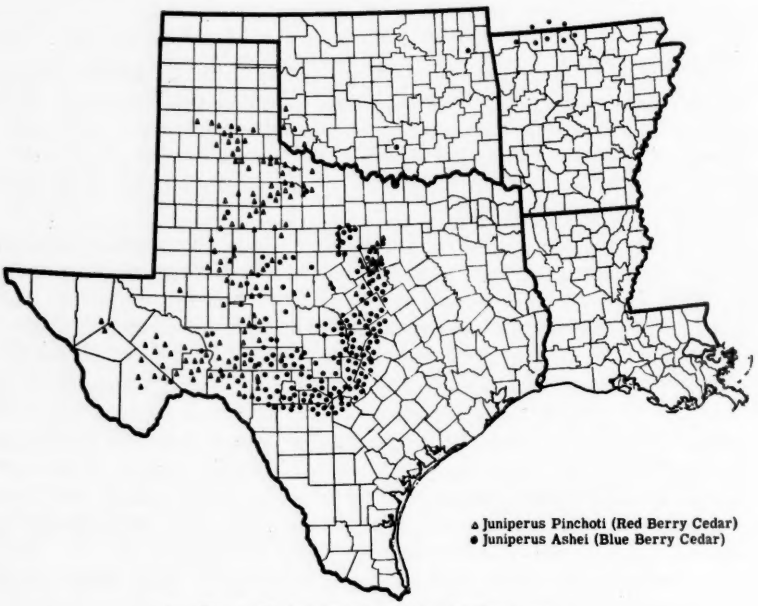

Fig. 1. Juniper distribution in the Southwest.

Leaves.—Opposite or in threes, thickened, rounded and glandular on the back, denticulately fringed, drab-green in a mass, on vigorous shoots very slender, thin and sharp-pointed, the gland elongated and resembling a midrib. The glands on the one and two-year-old wood rupture easily, leaving a white spot of wax when dry.

Flowers.—On separate plants. Pollination occurs from late September to late November.

Fruit.—Copper-red or reddish brown, globe-shaped, ripe one year after being pollinated, very variable in size, averaging ¼ foot in diameter, with thin skin and thick, mealy or juicy, sweet flesh and one or two seeds. Seed egg-shape; very blunt or truncate at apex, upper part lustrous brown and marked with several grooves above the two-lobed, prominent, speckled hilum. Embryo with two cotyledons.

Twigs.—Uusually reddish in the fall, thick on slow-growing wood, slender and often drooping when rapidly elongating.

Bark.—Thin, persisting as thin anastomosing scales.

Wood.—Heartwood brown or light brown. Sapwood nearly white.

Habitat and Distribution.—Rocky hills, stream breaks, valleys and divides in alkaline soils from Fort Worth, Texas, south to Bandera and Uvalde Counties, west to

near Alpine, Texas, and northwest into southwestern Oklahoma and the lower Panhandle of Texas. Largest known areas in Texas by groups of counties are in Hood, Bosque and Somervell Counties; Val Verde, Crokett, Terrell, Pecos, Irion, Tom Green and Schleicher Counties; Glass Mts., Coke, Sterling, Howard, Mitchell,

Fig. 2. Branches of male and female *Juniperus Pinchoti.*

Nolan and Taylor Counties; Garza, Kent, Stonewall, Crosby, Dickens, King, Knox, Foard, Cottle, Childress, Hall, Briscoe, Armstrong and Randall Counties. The largest areas lie west and north of the main body of mountain juniper. There are approximately 8,000,000 acres of redberry juniper in Texas.

Physically, the most outstanding differences between this and the post or mountain juniper of central Texas are: (1) it has red, not blue-black, fruits with a waxy bloom; (2) the pollination period is from late September to late November, not from December 10 to February 1; (3) the plants never have a central stem; mountain juniper usually has a central stem; (4) the glands of the leaves rupture leaving spots of white wax; they never rupture in the mountain juniper; (5) when the stems are cut, or burned off, new ones sprout from the bud zone or stem collar near the groundline; mountain juniper never sprouts.

We believe the above description is somewhat more accurate than that given by Sargent[9] in his *Manual of Trees of North America,* particularly in that Sargent failed to mention the bud zone or stem collar just above or at the groundline. This feature was not overlooked by Sudworth in his original description.

The pollen grains are uniform in size and spheroidal when moist. Upon drying they shrink and collapse irregularly. Grains when moist are 25 to 28 microns in diameter, and when dry 22 to 23 microns. In general they resemble *J. ashei,* but are somewhat larger.

We feel that there is a very close antigenic similarity between the blue berry and the red berry junipers. They may be antigenically identical. Kahn[6] and Black[1] have shown the very close antigenic relationship between two cedars which are botanically much less related than are the two under discussion. However, we have encountered at least two patients who have cedar hay fever only when the red berry cedar is pollinating, and these patients got better results from hyposensitization to the Pinchot cedar than they did when treated with the ashei extract.

Skin tests show a close parallelism, but just as there are variations in the degree of reaction to the various grasses and ragweeds, so there is some variation in the response to skin tests to these cedars. For practical purposes, we feel that the antigenic relationship is close enough to consider the extracts interchangeable in testing and treatment.

The fall-pollinating species is not as abundant as the winter-pollinating species of cedar and hence is not so great a problem in the eastern part of the Texas cedar belt. However, in several areas of southwest and west Texas, Pinchot cedar is present in much larger quantities than ashei, and it is increasing materially both in density and in area. It promises to increase even more—for while other cedars can be killed by burning over or by cutting above the ground, Pinchot cedar readily regenerates from roots or stump. Hence, we may find an increasing amount of hay fever from this cedar. Also, if it becomes widespread, it will extend our cedar pollen season from the latter part of September, when red berry cedar begins to pollinate, to the latter part of February, when blue berry cedar pollination ends.

SUMMARY

A cedar, the red berry juniper (*Juniperus Pinchoti,* Sudworth), has been found pollinating from late September through November, and is known to cause hay fever. Its distribution includes central and western Texas and adjacent Oklahoma.

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(Continued on Page 441)

ECZEMATOUS CONTACT DERMATITIS DUE TO STREPTOMYCIN

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VARIOUS types of "toxic erythemas" have been reported following the injection of streptomycin,[1] but, thus far, no instance of eczematous contact dermatitis has been noted.‡ We are therefore recording an example of the latter type of sensitization, in which the evidence pointed definitely to streptomycin as the cause. Involved in such sensitization are some points of considerable interest.

CASE REPORT

A nurse, sixty-three years old, had worked in a sanatorium for tuberculosis since April, 1946. In the early part of December, 1946, an eczematous eruption appeared on the dorsa of the fingers of both hands. Towards the end of January, 1947, the rash began to spread to the dorsa of the hands, forearms, lower parts of the arms and, to a lesser degree, the face and neck.

Examination revealed a diffusely erythematous, scaling and lichenified eruption on the dorsa of the fingers and hands, the flexor aspects of the forearms, and the antecubital spaces, the eruption ending at the lower portion of the arms. The face and neck showed only a few fading lesions. The palms, feet and toes revealed no abnormalities.

The morphology of the eruption, its diffuseness and its distribution were features characteristic of eczematous contact dermatitis. This was further supported by the somewhat greater intensity of the eruption on the right upper limb (the patient was right-handed) and by the abrupt termination at the lower portion of the arms just below the point where the short sleeves of her uniform ended.

Among the substances which the patient had handled in the preceding three or four months were: codeine phosphate, morphine sulfate, tincture of green soap, ethyl alcohol, Brown mixture, Stoke's Expectorant, Pond's Cold Cream, and, very occasionally, Demerol hydrochloride. In addition, she had been injecting nightly about twenty-five tuberculous patients with a solution of streptomycin and, at the conclusion of this procedure, she had cleaned out all the syringes containing this substance. About ten days after she began to inject streptomycin solution, an eruption was noted on the fingers of the hands, with the clinical course as already described.

The patient was advised to stay away from work until the precise cause could be determined. This she refused to do for sundry reasons. However, she did take a short vacation of four days, and, on return to work, she used rubber gloves whenever streptomycin solution was handled. When she returned for patch testing about a week later, the eruption had almost completely disappeared.

Patch tests were applied for forty-eight hours in the following concentrations: codeine phosphate, morphine sulfate and Novocaine, each 1 per cent; Demerol hydrochloride, 2.5 per cent; streptomycin hydrochloride, 10 per cent; ethyl alcohol, 95 per cent; and Brown mixture, Stoke's Expectorant, Pond's Cold Cream and tincture of green soap, each undiluted. All the patch tests were negative, except for streptomycin hydrochloride, which showed a broadly erythematous, edematous and slightly papular reaction (graded about 2 plus), and Demerol hydrochloride, which elicited an erythematous and edematous response (graded 1-2 plus). The sites of these positive responses (the streptomycin and Demerol patches were adjacent to one

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‡This statement was true at the time we submitted this article for publication. Since then, a number of instances of streptomycin eczematous contact dermatitis have been reported by other observers.

another) had caused severe itching some ten to twelve hours after the patches were applied, the itching being sufficiently intense to awaken the patient from sleep.

In order, further, to show the specificity of these reactions, six control subjects were patch-tested with streptomycin and Demerol in the same concentrations. The results were negative. This evidence indicated, therefore, that the concentrations used were not primarily irritating to skin and that the positive responses in our patient were based on specific hypersensitiveness to these substances.

Since positive reactions were obtained with both streptomycin and Demerol, the question arose of whether the eruption was caused by one or both substances. The patient stated that she had handled Demerol very infrequently, the last date of contact being at least two weeks before the rash spread to the forearms, arms, face and neck. Contrariwise, the lesions had first appeared about ten days after she came into active and prolonged contact with streptomycin, and, with continued handling of the substance, the cutaneous lesions became more intense. As soon as the patient stopped handling streptomycin and also used rubber gloves, the eruption began to improve.

During the following month the patient again handled streptomycin solution. Although rubber gloves were continuously used, she was not careful in the way she carried out her duties. The eruption was much improved, but there were periods of mild intensification. Owing to an accident, she was forced to quit work for two weeks, and during this time the cutaneous lesions disappeared completely. On return to work, the eruption with its attendant severe itching recurred in a few days on the forearms, between the fingers and on the face. During this period she had handled *only* streptomycin solution. She admitted that she was careless in the use of the rubber gloves; for example, she had worn torn rubber gloves on several occasions. Moreover, it was a common occurrence for the patient to be splashed by the streptomycin solution while injecting it, and this had occurred on the exposed parts of the upper limbs as well as on the face.

Physical examination a few days after the eruption recurred disclosed diffuse, lichenified eczematous patches on the flexor surfaces of the forearms, with similar but more intense involvement of the antecubital spaces. There were similar eczematous areas of moister character in all the interdigital webs and along several fingers of each hand. There was also a mild scaly eczematous area, the size of a nickel coin, on the right side of the face near the lips. We wish to stress the point that during this period of recurrence, the patient had not handled Demerol hydrochloride, this duty having been taken over by another nurse.

Since the solution of streptomycin hydrochloride that had been used for the preceding patch tests was impure or relatively impure, the problem at this point was to determine whether the eczematous contact dermatitis was caused by streptomycin itself or by some impurity in the preparation. For this purpose we obtained a specimen of pure streptomycin in the form of a double salt (white, *crystalline* substance).*

Patch tests with this pure streptomycin, in concentration of 10, 5 and 2 per cent solutions, showed the following results in twenty-four hours: 10 per cent, a widely diffused, erythemato-papular reaction (graded 2 plus); 5 per cent, a more localized erythematous and edematous response (graded 1-2 plus); and 2 per cent, a mild erythema (graded plus-minus). It may be noted that the patient complained of severe itching in the patch test area, the sensation being localized definitely at the site of 10 per cent streptomycin solution. On the next day the reactions were more intense and ranged from 2-3 plus for the most concentrated solution to 1-2 plus for the least concentrated solution of streptomycin. Ten control subjects were patch-tested with these concentrations of streptomycin solution, the results being uniformly negative.

*Streptomycin calcium chloride complex, Lot No. 7F1543, was supplied by the Medical Division of Merck and Co., Inc., and assays 759 units per milligram.

DISCUSSION

Although the clinical data in the first attack of eczematous contact dermatitis favored definitely streptomycin as the cause of the eruption, the occurrence of a positive patch test with Demerol militated against drawing an absolute conclusion. However, the subsequent course established beyond any doubt that the eczematous contact dermatitis was caused by streptomycin.

Throughout the history of eczematous contact dermatitis, particularly since the nineteenth century, there has been a tendency to implicate impurities as the cause of such eruptions. In practically all instances this idea has not been substantiated by subsequent events. In the case which we have recorded, the same theory of impurities in the streptomycin might have been reasonably entertained, but patch test studies with a specimen of pure streptomycin showed definitely that the eczematous contact dermatitis was caused by streptomycin itself or, possibly, by its break-down products.

Streptomycin has been characterized chemically as a complex substance ($C_{21}H_{39}N_7O_{12}$), composed of an amine-substituted disaccharide (streptobiosamine) that is linked to a 1,3-diguanidino-2,4,5,6-tetrahydroxycyclohexane (streptidine).[2] The streptidine portion of the molecule can be split off by acid hydrolysis.[2] If the sensitization to streptomycin should prove to be due to the whole molecule, this would provide the first example, as far as we know, of *eczematous contact dermatitis caused by a chemical containing a sugar radical.* It is of course possible that streptomycin is split by enzymatic action in the skin to liberate streptidine and streptobiosamine. If this should occur, streptidine would be more likely, in our opinion, to be the offending agent for two reasons: (1) eczematous contact dermatitis due to sugar molecules *per se* is unknown† and is most unlikely to occur with such substances, although we realize that the disaccharide streptobiosamine contains a substituted amine group; (2) the streptidine molecule contains two guanidine groups, and certain guanidine derivatives are known to cause eczematous contact dermatitis.

The chemical data thus far reported would seem to negate the possibility of a group or cross-reaction between streptomycin (or any possible break-down product) and Demerol, since in the former the chemical structure is that of a diguanidino-cyclohexane-disaccharide, whereas, in the latter the structure is that of a substituted piperidine molecule. These compounds seem to be too far apart chemically to postulate a cross-reaction. It appears more probable that our patient had two independent sensitizations.

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†The so-called sugar itch, which has been known since the early part of the nineteenth century and before, is a heterogeneous concept. Cases falling within this category have not been shown to be based on the mechanism of sensitization to the sugar molecule.

SUMMARY AND CONCLUSIONS

We are reporting what seems to be the first instance‡ of eczematous contact dermatitis due to streptomycin. Data are given to show that this substance in a pure form is capable of inducing this type of sensitization. If this type of sensitization is caused by the whole molecule, this would provide the first example of eczematous contact dermatitis due to a substance containing a sugar radical. It is possible, however, that the sensitization is due not to the disaccharide portion of the molecule (streptobiosamine) but rather to the streptidine portion of the molecule (diguanidinotetrahydroxycyclohexane). This would presuppose the possibility that streptomycin can be split into these two major components by an enzymatic action on the part of the skin.

Nurses and others who handle streptomycin should use rubber gloves as a precaution and should avoid prolonged contact with this substance on the skin.

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TREATMENT OF ALLERGIC AND OTHER DERMATOSES WITH PYRIBENZAMINE HYDROCHLORIDE

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BROMOTHEN AND CHLORTHEN—5-BROM-2-THENYL AND 5-CHLOR-2-THENYL DERIVATIVES OF THE ETHYLENEDIAMINE GROUP

Preliminary Report

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TO solve the riddle of treating allergic manifestations, the approach has been to tackle the allergen-reagin reaction. Most research is based on the histamine theory. The development of antihistaminics followed. Benadryl and Pyribenzamine have contributed much to palliative relief of allergic symptoms, but each has an extremely high incidence of side effects which are objectionable.

Litchfield and his co-workers[1] at the Stamford Research Laboratories have halogenized the ethylenediamine group (N, N-dimethyl-N'-2-pyridyl-ethylenediamine). They claim that this compound is much less toxic and much more effective than Pyribenzamine.

These compounds for convenience were labeled Bromothen* and Chlorthen†. It was of interest to try these compounds to determine if the incidence of side effects (especially dizziness, drowsiness, tiredness) could be markedly reduced or eliminated. Therefore, twenty-six patients were chosen who had experienced these side effects from Benadryl and Pyribenzamine. These patients had urticaria and allergic rhinitis, and although they obtained relief, they could not continue therapy because of the uncomfortable side effects. Of this group, eighteen patients were given Chlorthen and eight were given Bromothen. All experienced relief of symptoms within fifteen minutes to half an hour after taking 50 milligrams. None had any side effects whatsoever. The patients were put on 50 milligrams three times daily. Six patients had adequate relief from symptoms after one day's use. The rest had to continue for two or more days (up to six) to have their relief prolonged.

Since the number of patients was small (only twenty-six), a larger group was given these compounds. Twenty-five additional patients who had never had either Benadryl nor Pyribenzamine were given Chlorthen and twenty-two were given Bromothen. The symptoms complained of were pruritis, rhinitis, urticaria, eczema, coughing and wheezing. So far none have experienced any side effects. Relief of symptoms was obtained as expected. The group is being enlarged to include more in number and more in varied allergic manifestations. Thus, material will be available for more detailed analysis to be reported at a later date.

This is in the nature of a preliminary report. This is not intended to

(Continued on Page 441)

Bromothen and Chlorthen supplied through courtesy of Lederle Laboratories.
*5-brom-2-thenyl-N, N-dimethyl-N'-2-pyridyl-ethylenediamine.
†5-chlor-2-thenyl-N, N-dimethyl-N'-2-pyridyl-ethylenediamine.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

REACTIONS AND THEIR SIGNIFICANCE

Scientific papers are sometimes more important for what is incidental than for the original thesis. In the studies conducted by Cowan and Diehl, at the request of the Commission of Influenza of the Office of the Surgeon General, 666 students of the University of Minnesota were used as subjects. Of these, 346 received 1 c.c. of standard influenza A and B virus vaccine. A control group of 320 students was given 1 c.c. of physiological saline.

The severity of the colds seemed equal in both groups, their numbers being 2.9 colds for students who were vaccinated as compared to three for the controls. The complications were 19.8 per cent for the vaccinated and 21.0 per cent for the controls. Infirmary care was necessary for 1.6 per cent of the vaccinated students and 2.9 per cent for the controls.

The incidental finding, however, is of great importance to every worker in the field of injection therapy. Since none of the students knew the nature of the material injected, the study was an excellent test as to whether the material caused the reactions. In the vaccinated group, reactions were reported in 83.8 per cent of the students. But, in the unvaccinated group, the students receiving 1 c.c. of sterile physiological saline reported reactions totalling 22 per cent, more than one in five.

If the injection of 1 c.c. of physiological saline can cause reactions in more than one-fifth of the subjects, the effect of suggestion and of psychotherapy in injection treatment cannot be underestimated, if it can be estimated at all.

THE ALLERGEN OF HOUSE DUST

Although house dust is one of the most frequently used antigens in the therapy of the allergic patient, there is very little that has been determined quantitatively of the nature of the active constituent. A start in this direction has been made by Rimington, Stillwell and Maunsell. In the *British Journal of Experimental Pathology* (28:309, 1948), it is shown that a purified antigen which gives positive reactions in sensitive individuals can be prepared from house dust. This contains about 25 per cent hexose and 2.5 per cent nitrogen. Acid hydrolysis liberates a reducing sugar, probably galactose, and some simple amino acids. Tyroine and histidine are absent. Milder acid hydrolysis liberates 80 per cent of the carbohydrates but no

amino acids. An antigen remains with undiminished activity containing 12 per cent hexose and 10 per cent nitrogen. It is of interest that the antigen before or after the mild hydrolysis shows two main components electrophoretically: one mobile and colored, and the other immobile and colorless. These are similar in composition, to a certain extent, and also in antigenic potency. It is of interest that these pioneer electrophoresis experiments with dust show similar results to those which have previously been reported in detail with the electrophoretic fractionation of the pollen antigens. Thus, in all of the pollen antigens investigated thus far, there are essentially immobile, colorless antigens with a number of pigments colored and mobile. Further investigations of this type with purified allergens, in all likelihood, will provide a better immunochemical basis for the behavior of the sensitized individual.

The same authors (Stillwell, Rimington and Maunsell) in a second paper show that a general similarity exists between polysaccharide products derived from molds and preparation of the house dust antigen. They are all, like the main pollen allergens, of polypeptide structure associated with a polysaccharide complex. The pollen allergens have been designated as "protoproteins," that is, intermediate in size between the polypeptide molecule and protein. We can look forward to further information on the nature of these dust allergens when their molecular weights are determined in the ultracentrifuge. By these modern techniques, much of the obscurity connected with pollen allergens and a good deal of the confusion will be ultimately eliminated.

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BROMOTHEN AND CHLORTHEN

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be a study to draw adequate conclusions, but the results were such as to warrant the formation of a larger group with other allergic manifestations for further study. A report on the results obtained will be made on a sufficiently larger series of cases to draw adequate conclusions.

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Progress in Allergy

ALLERGIC SKIN DISEASES
Review of Recent Literature

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Atopic Dermatitis
(Neurodermatitis Disseminata)

Analyzing our present and past concepts of atopic dermatitis and summing up what is known concerning its immunologic background, A. Rostenberg, Jr.,[4] states the following facts:

1. Many individuals give multiple positive immediate whealing reactions to protein substances.
2. These substances do not seem to influence the course of the dermatitis; exposure to them usually does not cause an exacerbation, and their elimination does not lead to improvement.
3. Individuals with atopic dermatitis yield positive patch test reactions to protein or to heavy metals.

The nature of these reactions is unknown, but they signify some sort of dermo-epidermal sensitivity other than the wheal type. In order to weld these facts into a single immunologic theory which is consistent with the clinical observations, Rostenberg suggests the following hypothesis of a dual hypersensitivity:

1. Individuals with atopic dermatitis have an immediate wheal-type sensitivity. Consequently they will have an antigen-antibody reaction. The effects of such a reaction are alteration of capillary permeability and release of histamine and probably other substances.
2. A dermo-epidermal sensitivity exists in these individuals either to the same or different allergens. However, these allergens cannot get to the epidermis or cannot make their effects manifest in the epidermis until the "capillary door" is opened to them by the alterations in capillary permeability, which results from the wheal-type of reaction.

Rostenberg has made a worth-while attempt to correlate the immunologic background and clinical observations in atopic dermatitis. The situation is still rather confusing; there are too many unknown factors and contradictory opinions. The causative significance of the "atopic" allergens in atopic dermatitis is not yet settled; their role had been overemphasized previously; at present the pendulum seems to swing too much in the other direction.

There are cases of atopic dermatitis that can be reproduced by exposure to the allergen which produced an immediate whealing reaction. Rostenberg's vascular theory explains perhaps why this seems more often the case in localized atopic dermatitis when the allergen penetrates the skin from without (Hill's atopic dermatitis by contact). I may mention in this respect some cases of atopic dermatitis from pollens; those cases of "milker's eczema"[2] that are due to cattle sensitivity, and instances of "baker's eczema," which are accompanied by whealing reactions to wheat.* Of eight cases of baker's eczema among 653 bakers in Finland, Kilpinen[3] reported four that gave positive whealing reactions to wheat and also to rye and barley. There was no reaction to the flour-improving substances.

Most observers will probably agree with Rostenberg that the pathological and clinical discrepancy between a chronic atopic dermatitis and a chronic contact eczematous dermatitis is really not very great. However, these instances of chronic dermatitis are probably of a more complex and complicated nature. Atopic dermatitis has been viewed too much from the atopic angle, and contact dermatitis too much as a mere eczematoid sensitivity. There is little known about their in-

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*Baker's eczema may be caused by a variety of factors. Some of the cases apparently are contact dermatitis with hypersensitivity to the substances added to improve the flour, especially persulfates.

terrelationship. Two competent observers present opposite views. Tolmach's[7] impression is that the atopic individual is not more easily sensitized in industry than the so-called normal people. In Downing's[7] experience, however, atopic individuals should not work where they will contact sensitizing chemicals.

According to Rostenberg, in atopic dermatitis there is an epidermo-dermal sensitization other than the wheal type. What the allergens may be is still an open question. Simon's work on the role of human dander is well known. Recently[6] he found that the allergen of human dander is also present in skin of the general body surface, although extracts from the scalp dander were much more active allergenically. The identity of the allergenic principle of dander and normal skin was proven by passive transfer experiments and neutralization of reagins.

Weedon[8] believes that common intestinal fungi may be the source of allergens in certain severe cases of chronic atopic dermatitis. The stool specimens of ten individuals examined showed heavy growths of yeastlike fungi—Candida albicans occurring once, Candida tropicalis once, Geotrichum four times—and other yeasts not yet identified, as well as heavy growths of various molds. Eight patients were treated with fungicides and showed great improvement. Potassium iodide by mouth effected striking improvement temporarily in two patients, but in one of these the initial dose was followed by a severe temporary exacerbation of the disease. Seven patients were treated by inunction with phenacyl iodide 1:1,000 over the thighs and cautiously over the lesions. None of these showed exacerbation, and all steadily improved to total or near total freedom from eczema. In most cases the number of yeast colonies in consecutive stools decreased with treatment.

In this connection one is reminded of Guiz-Moreno's[5] eczematoid monilid. From the clinical description his cases seem to fit in with localized atopic dermatitis of the neck and eyelids; the author, however, believes this condition is not atopic, as it was not possible to prove the presence of reagins. The eczematous syndrome usually affects women and is localized on the eyelids, lips, and neck, where it appears as a dry, scaly and pruritic dermatitis, usually in the spring and fall. Patients show both immediate and delayed reactions to intradermal tests with a potent extract of C. albicans. Guiz-Moreno considers the condition a special and frequent manifestation of a monilid. There is absence of mycotic infection at the site of the rash; positive delayed reactions to an extract of C. albicans indicate an "infectious" or "tuberculin-type" allergy; exacerbation follows the injection of an excessive quantity of the extract; therapeutic administration of the extract subcutaneously produces complete cures; and an intestinal focus of C. albicans is demonstrated. In treating these patients with an extract of C. albicans, the curative dose varies widely, from 3 to 1,000 Coca units. Often the curative dose is very close to the reaction-producing dose.

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Infantile Eczema

According to Ratner[3] best results in the management of eczema in children are obtained if the condition is viewed from the standpoint of diet, environment, psychosomatic and constitutional phases, in conjunction with local dermal therapy.

Infantile eczema is the prevailing allergic condition in infancy and is the earliest of all the allergic syndromes. In Ratner's experience the average age of onset was one and nine-tenths months. Positive allergic skin reactions were obtained in 85 per cent of the patients under one year of age. All of these positive reactors were sensitive to foods, but only 41 per cent of them reacted to foods alone. Fifty-nine per cent reacted to a combination of foods, inhalants and contactants. Ratner uses the following procedures prior to skin testing. The child is placed on a diet of allergenically denatured foods such as evaporated milk, pablum, pabena, thoroughly cooked cereals and vegetables, thoroughly boiled meats, hard boiled eggs and stewed fruits. A dustproof environment is recommended, animals should be removed.

For local treatment Ratner lists the commonly used antieczematic measures. For secondarily infected, wet, oozing skin a 2 to 4 per cent aqueous solution of gentian violet at times proves the most gratifying compound. Phenobarbital in small doses and acetyl salicylic acid in 3 to 5 grain doses, or their combination, are the sedatives of choice. The antihistaminic drugs allayed the pruritus only to some extent in Ratner's experience, whereas Wolpe[5] found that Pyribenzamine gave great relief from itching in a large number of cases.

Wolpe[8] presents in detail the management of infantile eczema as practiced at the Los Angeles County Hospital. The reader is referred to the original. In contradistinction to Ratner[3] who does not differentiate between atopic dermatitis and contact dermatitis in children, Wolpe follows a modification of the Hill-Sulzberger classification of infantile eczema. Wolpe deplores the attitude of many clinicians that eczema may be ignored because "it will sooner or later clear." By proper treatment much misery on the part of both infant and parent can be avoided. It has been Wolpe's experience that itching persists for some time after the skin has completely cleared. He believes that if restraints are discontinued less than two to three months after clearing, traumatic relighting of the eczema is probable. The allergic management is carried out by placing the child on a very restricted diet, and putting it in an environment as dust-free as possible. Skin testing is not mentioned in his paper. For various reasons, and because Wolpe feels that there is a "growth factor" in milk, he has attempted to maintain the patient on milk for at least one week. In another study, Wolpe[6] found, however, that babies fed milk substitutes reach clinical relief faster than those fed on a milk diet. Wolpe[7] also observed that nutritional crises, characterized by edema, dehydration, apathy, listlessness, anorexia, profuse diarrhea, or actual prostration, occurred in infants suffering from severe generalized eczema. Routine weekly hemoglobin and albumin-globulin determinations revealed a startling incidence of hypoproteinemia. This was recognized as being frequently present with deficient food intake, such as in presence of elimination diets and/or failure of complete absorption, and with excessive food loss, such as with allergic diarrhea. In a series of fifty-four cases of infantile eczema, 26 per cent revealed a protein deficiency. In these the globulin fraction showed a greater percentage of deficiency from normal than the albumin fraction.

The therapy consisted of (1) liver extract 0.5 c.c. (7.5 units) to six months and 1.0 c.c. over six months of age, intramuscularly twice weekly; (2) vitamin B complex 1.0 c.c., intramuscularly twice weekly; (3) intravenous plasma; (4) intravenous blood alternated with plasma when hemoglobin value was low: (5) one tablespoon twice daily of hydrolyzed amino-acid mixtures; (6) dietary elimination.

One of the most dreaded complications of infantile eczema is the so-called Kaposi's varicelliform eruption. Cases are reported by Barker and Hallinger,[1] Lynch and Steves[2] and Ruchman, Welsh and Dodd.[5] According to Ruchman et al, Kaposi described a syndrome, occurring in children who had a pre-existing atopic dermatitis, which was characterized by recurrent crops of lesions that went through stages of vesiculation, umbilication, desiccation and rupture; when these lesions healed only the signs of the original atopic dermatitis persisted. Juliusberg described a fatal case in which there were similar lesions to those described by Kaposi under the title of "pustulosis acuta varioloiformis." An eruption similar to the one described by Kaposi has been noted in individuals exposed to recently vaccinated members of the family, or who have themselves recently been vaccinated, and in many of these cases the vaccine virus was recovered or the Guarnieri bodies were demonstrated. Recently the virus of herpes simplex has been isolated from several patients presenting this syndrome, and it is now thought that there are at least two causes for these similar eruptions—one caused by the virus of vaccinia and known as eczema vaccinatum, and the other caused by the virus of herpes simplex and known as Kaposi's varicelliform eruption. There have been ninety-six cases of this condition reported in the literature, and of these, seventy-five occurred in children and only twenty-one in adults. The authors report four additional cases, three occurring in adults and one in an infant aged fourteen months. All four patients gave a history of a definite exposure to the virus of herpes simplex from five to ten days prior to the onset of their eruption, and none knew of any exposure to the virus of vaccinia. Strains of herpes simplex virus were isolated from the cutaneous lesions of all four patients. The antibody titre increased during convalescence in two of the adult patients, but in the one fatal case, which occurred in an adult, there were no antibodies during the acute stage of the eruption.

Riley and Callaway[4] feel that although similar clinical pictures appear in eczema vaccinatum and Kaposi's varicelliform eruption, there are sufficient differences to suggest the diagnosis without laboratory procedures. They point out that in eczema vaccinatum there is usually a history of vaccinia contact, while in Kaposi's varicel-

liform eruption there is a history of herpes simplex contact. In eczema vaccinatum the lesions go through typical stages of a vaccinia eruption, while in Kaposi's varicelliform eruption they may be similar in some cases, but they usually are typically herpetic, and frequently the grouping is characteristic of herpes simplex. Additional points of differentiation between these closely related conditions are tabulated. To definitely establish the diagnosis, virus studies are at times necessary. The authors report two cases of eczema vaccinatum in which there was a definite history of exposure to vaccinia, and in which virus studies were carried out.

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Psychosomatic Aspects

Although psychologic influences may play some role in various eczemas, they are more important in atopic dermatitis. A study of the automatic nervous system in "atopic" individuals is presented by Cohen and Wolf.[2] The clinical observation of increased palmar sweating in disturbances of the autonomic nervous system has long been recognized. A significant increase in the incidence of intensive palmar sweating in anxiety has been demonstrated. Patients with allergic-respiratory disease, mostly bronchial asthma, manifested a statistically significant increase in the incidence of intense palmar sweating. Cohen and Wolf believe that clinically manifest allergic-respiratory disease in man is dependent on an inherent behavior pattern of the autonomic nervous system in addition to the immunologic factor of hypersensitivity. (Such a study might also be worth-while in regard to patients with atopic dermatitis.)

Woodhead[10] reports a psychologic study of a group of twenty-six children and young adults suffering from eczema, atopic dermatitis and papular urticaria. They had resisted regular treatment, but were cured by psychotherapy. Woodhead found often unconscious psychologic problems in the parents, affecting the child as well as psychologic difficulties of the child itself. The children are generally abnormally gifted, energetic, determined, aggressive and egotistical to the point of narcissism. In addition they are frightened and unsure because of great sensitivity. The healing of the skin disease runs parallel with the successful psychological treatment. There is a tendency to slight relapses during the treatment, when faced with difficult situations. The skin disorders are a reaction to an unfavorable environment or to a psychological shock. The author recommends an early and careful psychological treatment of the child and of the parents to avoid allergic reactions becoming permanent.

Schneider and Kesten[7] studied ten cases of what they call polymorphic itching dermatitis or polymorphic prurigo. This condition corresponds to that previously described under such various names as generalized erythroderma, distinctive exudative discoid and lichenoid chronic dermatosis, and allergic dermatitis simulating lymphoblastoma. According to these authors, this dermatologic syndrome, while difficult to define, has become recognized as a fairly distinct clinical entity. The etiology remains obscure, although a history of personal or family allergy is usual. Severe and uncontrollable itching, together with the prevalence of emotional disturbances, has been stressed in most of the previous studies. Hospital care and permanent residence in a sunny dry climate are beneficial. Psychosomatic studies of Schneider and Kesten's cases indicated an etiologic relationship between emotional conflict of the patients and their dermatitis. While in a state of marked anxiety and guilt related to a particular conflict, an individual develops a mild localized dermatitis that may be or may simulate one of the common dermatoses. This simple dermatitis may go over into a severely pruritic polymorphic recalcitrant dermatitis because of the concomitant effective disturbance of the autonomic control of the skin. Etiologically many factors are probably impli-

cated, of which the psyche is only one, but its paramount importance is indicated by the major position that psychotherapy occupies in successful treatment.

After some months' residence in the southwest away from unsatisfactory emotional environment, seven patients became free from this eruption. Of this group, five have remained in the southwestern states and are ostensibly cured. The other two patients returned to the east, one to her old surroundings, where she has had a recurrence of the eruption, the other to an emotionally satisfactory environment where he has remained well. The remaining three patients underwent a psychosomatic study. After therapy two of the three have remained well while living in their habitual environment. This study indicates that emotional conflict is of singular importance in the evolution of polymorphic prurigo and that psychotherapy is a major factor in its successful treatment.

According to Robertson,[6] patients with intractable dermatitis may sometimes be found to labor under a deep sense of grievance. Inquiry into the emotional difficulties associated with the onset of the dermatoses may cause an acute exacerbation. The technique of treatment should be directed toward extirpating a sense of injustice from the patient's emotional life.

Forman[4] used Evipan in the investigation of twenty military patients who presented recurrent and chronic dermatoses. Progress had been unaccountably delayed; in many cases symptoms and signs were exaggerated. Evipan was slowly given intravenously in a 1 per cent solution until the first stage of anesthesia was reached. Usually 0.4 gm. was sufficient. The patient was then questioned, and any answer that appeared of significance was pursued. If replies became guarded, or ceased, more Evipan was given until the patient was again relaxed and sleepy, resistance to questioning was removed, and the answers again given freely. There apparently was no period of amnesia following such procedure.

With suitable doses of the barbiturate, intellectual criticism and emotional control were removed. The patients had a feeling of confidence and a desire to communicate. Intimate questions were answered freely, and a surprising depth of mental processes and emotional content were revealed. The information gained during these procedures was used in subsequent discussions with the patient to further his understanding of the relationship between his difficulties or conflicts and his cutaneous disease.

The author's clinical diagnoses in these cases were lichenification, excoriated dermatitis, urticaria, pruritus, and dermographism. Following Evipan, the cases were regrouped as anxiety state, purposive conflict, maternal attachment, depression, and paranoid. The author points out that a short "narcoanalysis" under Evipan cannot take the place of a careful personal history by a trained psychologist and of his evaluation of personality and the effects of mental trauma. Evipan narcosis offers a quick and probably reliable method of psychologic investigation, particularly if the services of a psychologist are not readily available.

Walsh and Kierland[9] treated fifteen patients with atopic dermatitis (generalized neurodermatitis) with psychotherapy. These patients had failed to respond satisfactorily to dermatologic treatment. Certain characteristic emotional patterns were noted, of which the authors consider the following the most prominent ones: "Suppressed hostility toward the mother or a mother figure was present in most. The skin was apparently utilized in these patients as a site for expressing strong unconscious conflicts relating to exhibitionistic tendencies and a frustrated desire for love and affection. The possibility exists that the mutilation of the skin by scratching and excoriation may have had the significance of self-punishment or partial suicide. This was thought to be related to guilt feelings resulting from hostility and death wishes toward the mother or mother figure in most if not all of the patients. The patient thus, in fact, made himself unlovely, which may correspond to his feeling that he was unworthy to be loved or even unlovable. There was a strong tendency in all of these patients toward the handling of strong emotion through suppression. In all of the patients whose dermatitis had begun in adult life, it had been preceded more or less immediately by a frustrating experience. In the five patients whose dermatologic reaction had begun in childhood, the emotional disorder appeared deeply rooted in the personality, and striking results from psychotherapy were not obtained. In three patients with marked depressive reactions, a series of electroshock treatments was also given, with one failure in a patient to whom effective psychotherapy could not be given because of language difficulty. With this one exception, improvement in the emotional disorder was paralleled by a complete or nearly complete clearing of the dermatologic reaction, and this improvement has endured during the period of observation in all patients whose dermatologic reaction had first appeared in adult life. Marked

improvement or disappearance of asthmatic symptoms concurrently occurred in the four patients in this group who had asthmatic syndromes."

According to Lewis and Cormia,[5] little progress has been made in the psychologic interpretation and management of the cutaneous manifestations of psychosomatic disease. The psyche unconsciously selects any convenient locus minoris resistentiae for the cutaneous expression of internal conflict. Bodily emotions symbolically expressed by the skin include those of worry (picking), anxiety (pruritus and sweating), fear and anger (urticaria), guilt and shame (blushing and rosacea), hostility, masochism and eroticism (dermatitis factitia) and sexual pleasure (cutaneous masturbation).

Such devices may directly aid in avoiding unpleasant reality by producing disability or a socially acceptable sublimation of a conflict. According to the classification of Lewis and Cormia, lichen simplex chronicus (localized neurodermatitis) and acute neurodermatitis are always psychogenic, but often with additional etiologic factors as well. Pruritus, urticaria, and dyshidrosis of hands and feet are frequently, but not always, psychogenic. As dermatoses which combine psychogenic and other etiologic factors, the authors classify atopic dermatitis (disseminated neurodermatitis), contact dermatitis, and dermatitis medicamentosa. Lewis and Cormia attempt a symbolistic interpretation of the underlying conflicts in patients with psychosomatic dermatoses. These conflicts are expressed by the type of lesions as well as by the localization. Here are some examples relating to eczemas: Lichen simplex chronicus—long-standing worry and anxiety with makeshift adjustments. Acute exudative neurodermatitis of flush areas—severe anxiety, acute or prolonged unsolvable conflicts. Atopic dermatitis—prolonged social resentment, hostility, compensatory aggression. Urticaria—acute phobias with anxiety, hostility, and anger. Examples of expression of psychosomatic conflict by localization are given as follows: Head (rosacea, seborrheic dermatitis, eczematous ear)—social anxiety, stigmatization, guilt. Hands and feet (pompholyx)—dislike or fear of occupational duties. Ano-genital sphere—sexual or domestic disturbances, maladjustments or frustration in these spheres.

The psychosomatic study of a dermatosis embodies all that is best in routine dermatologic and psychiatric care. It involves tracing the psychic and physical growth of a patient through his life span and constructing a basic personality pattern.[3] Prolonged, painstaking therapy is required. Best results, in Lewis and Cormia's experience, were obtained when both psychical and psychic measures were included. The purely symptomatic approach did not correct the underlying problems. In these instances, relapse, development of another "neurodermatosis," or psychosomatic complaints involving other organs would result almost inevitably. With the combined methods, the results were decidedly good: 50 per cent of the group were cured or markedly improved. Lewis and Cormia's views are not generally accepted. Sulzberger and Baer[8] state that there is no proof that psychic or neurologic factors are regularly of major importance in the various eczemas. The Freudian approach to psychosomatic disorders is outrightly condemned and called "unscientific" by Campbell.[1] He agrees that "inter-reactive influences which exist between the emotional, intellectual, and other bodily functions and the soma in its entirety, and reality outside the body should be taken into consideration," but stresses that "the complexity of these relationships should not be relegated to a group of fanaticists who have succumbed to the hypnotic technique executed by Freudians in the training of pupils and perpetuated by these trainees who have become and continue to become trainers of subsequent trainees, all of whom are under the spell of the systematized delusion of psychoanalysis."

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Contact Dermatitis

Mechanism of Eczematous Sensitization.—Landsteiner and Chase originally demonstrated in 1942 that cutaneous hypersensitiveness of picryl chloride may be transmitted passively to normal guinea pigs by intraperitoneal injection of cell suspensions obtained from experimentally produced peritoneal exudates in sensitized guinea pigs. Chase later showed that cells from the spleen and lymph glands are able to transmit this effect. Haxthausen[13] has confirmed these experiments using dinitrochlorobenzene and dixanthogen. He further demonstrated that cell suspensions of the thymus may also be used successfully. Thus, confirmatory evidence is furnished that cellular elements, especially lymphocytes, are carriers of the hypersensitiveness in contact dermatitis. Haxthausen also attempted passive local transmission with fresh lymphocytes and with extracts of such lymphocytes. Negative results were obtained in both guinea pigs and humans; in the latter, cells from the blood as well as from excised lymph glands were used. Hence, it is still an open question how the active principle in the lymphocytes is transmitted to the skin and by what manner they convey their specific capacity for reaction.

A working theory to explain the physiologic process of eczematous sensitization has been proposed by Rostenberg.[31] His theory embraces the work of many investigators, including himself. It is known that many substances are capable of causing an eczematous sensitization; yet experimentally only a relatively few compounds are regarded as reliable agents for reproducing this phenomenon with any degree of consistency. The explanation possibly lies in the persons rather than in the chemicals. There may be some peculiar genetic predisposition, or there may have been some special favoring circumstance, such as inflammation, at the time the allergen was encountered. It is also generally realized that the easiest route by which eczematous sensitization can be achieved is by application of the material directly to the skin, but this is not necessarily the only route. Rostenberg's theory holds that the eczematogenous allergen when applied to the epidermocutis reacts to form a new compound allergen. This substance appears to be a protein conjugated with the simple chemical or with some derivative of it. The compound allergen next leaves the skin primarily via lymphatic channels.[30] Six to nine days later the entire epidermis, as a rule, becomes sensitized. Practically nothing is known regarding the site of development of this hypersensitivity although this may occur in the regional lymph nodes. The antibodies formed are contained within the lymphocytes and possibly other cells. There are no humoral antibodies contained in centrifugal serum. However, if cells are involved in the passive transfer, the antigen-antibody mechanism may be demonstrated (Landsteiner, Chase, and Haxthausen). According to Rostenberg, two points about eczematous sensitization especially require elucidation. In the first place, why is the application of the allergen to the epidermocutis a superior route for the engendering of the sensitization; and secondly, what is the nature of the antibody formed and wherein does it differ from other more easily demonstrable antibodies? In regard to the first question, Rostenberg believes that the allergen has to be deposited at a site relatively rich in macrophages. The true cutis is such a site. He further believes that the ability to sensitize is increased if the compound allergen is insoluble (particulate). In response to the second question, Rostenberg emphasizes that the salient feature of the eczematous antibody is that it does not exist free in the circulation. It has a cellular affinity, probably as a result of the antigen incorporating a portion of the body's protein into its being, thereby increasing the specificity of the resulting antibody. A simple chemical then introduced to this sensitized tissue completes the eczematous reaction. From the foregoing, it is apparent there is still much work to be done on the physiologic mechanism of eczematous sensitization.

It has been shown by Miller[22] that contact eczematous dermatitis presents a definite and characteristic histologic picture by which it can be identified. The outstanding features of this disease are of two types, one resulting in necrosis of the epidermis and the other producing vesicular formation due to edematous degeneration of the prickle cells. The cutis shows congestion of the superficial blood vessels with a perivascular banal type of inflammatory exudate. Miller enumerated the essential points in the histologic differentiation of this disease from other members of the group of eczematous dermatoses.

Sulzberger[39] has expressed a preference for the name "allergic contact-type eczematous dermatitis" and has clearly defined and justified each word of his proposed designation for this type of dermatitis. He pointed out that aside from local dermatologic management, there is no specifie therapy other than discovery and elimination or reduction of the causative allergens. Sutton, Jr.,[41] has outlined his technique of eliminating and identifying an unknown irritant. All possible causes are removed and later reintroduced into the environment one by one. A

flare-up incriminates the substance last introduced. The author claims originality for this point of view. Patch tests are not undertaken, and guess work is eliminated.

Wodehouse[46] devised a system of measuring and recording the intensity of skin reactions. A "cutaneous reaction unit" is defined as a wheal 1 mm. in diameter surrounded by an erythema 1 mm. in excess of the wheal, or 2 mm. in over-all diameter. Intensities or reaction units may then be expressed by multiplying the wheal diameter by the excess of the erythema diameter over that of the wheal in millimeters or $n=w(e-w)$.

Eczematous Sensitization to the Antibiotics.—Eczematous sensitization may result from contact with either penicillin or streptomycin and constitutes an actual occupational hazard to those handling and administering these drugs. MacInnis[20] has reviewed the literature on allergic reactions from handling penicillin and has determined the incidence of the various possible reactions and their locations. Itching of the skin of the face, neck and body (indirect contact) is the most frequent response. She reported the histories of two nurses who developed symptoms other than dermatitis from handling penicillin. The first nurse had nasal congestion, itching, and whealing. The second had photophobia associated with conjunctivitis and edema of the eyelids. Hoffman[14] found that 40 per cent of his cases developed a contact dermatitis when penicillin wet dressings were used for more than four or five consecutive days.

An increasing number of reports in the literature testify to the fact that streptomycin is likewise a potent cutaneous sensitizer. Strauss and Warring[37,38] were among the first to call attention to this fact. They reported six cases of epidermal sensitization from streptomycin occurring among twelve nurses handling the drug. Four of these nurses presented a dermatitis; the other two were found to be sensitized on patch testing. Dermatitis developed after an interval of from one to three and one-half months after beginning exposure to the drug. These authors had little doubt that streptomycin itself and not an impurity was responsible for the sensitization inasmuch as the six subjects all reacted to two different lots of the drug and also to a preparation which was 98 per cent pure. Six cases of sensitization developing in twelve nurses indicated that the index of epidermal sensitization to streptomycin was high. Two additional cases of epidermal sensitization developing after prolonged exposure through handling of streptomycin were reported from another source.[44] Canizares and Shatin[3] reported three additional cases of contact dermatitis from streptomycin in nurses handling the drug, making solutions, and giving injections. Patch tests and intradermal tests with streptomycin were positive. The Report of the Council on Pharmacy and Chemistry[6] reported "more than a dozen instances" of contact dermatitis from the drug. Rauchwerger et al[28] reported six more cases among nurses. All were characterized by an initial erythema followed by a pruritus and a papulovesicular eruption. The pruritus was the most distressing symptom. In two cases there was actual denuding of the skin over the terminal phalanges of the thumb and index fingers of both hands, indicative of the more frequent exposure of these parts in handling syringes and needles. Five of the six subjects showed involvement of the periorbital areas, most probably a result of autoinoculation. These nurses were in intermittent contact with the drug for periods varying from eight to eighteen months, again demonstrating that sensitization develops only after prolonged exposure. Prophylactic measures for nurses administering the drug include the wearing of rubber gloves and frequent washing of the hands. Steam emanating from sterilizers in which needles and syringes have been sterilized should be avoided as this may furnish one source of exposure.[28]

Senturia and Broh-Kahn[32] treated fifty patients with otitis externa with an ointment containing from 250 micrograms to 5 mg. of streptomycin per gram of ointment base. No mention was made of any sensitization reactions.

Antihistaminics in Contact Dermatitis.—The question of the value of antihistaminics in the therapy of contact dermatitis is still unsettled.[2,21,24,28] There is a question whether the effect in this condition is due to the antihistaminic action of these drugs. According to Dreisbach,[8] central depression by these drugs or their local anesthetic action may be responsible for the subjective relief obtained. The controversy is discussed in the chapter on antihistaminics.

Formaldehyde-treated Starch.—Talcum powder, when introduced into traumatized tissue, is capable of producing a chronic inflammation of the granulomatous type. The risk involved in using talcum powder on surgeons' gloves is apparent and has

stimulated a search for a substitute powder. Potassium bitartrate was suggested and used, but it is not without shortcomings. More recently a formaldehyde-treated corn starch preparation has been introduced. The formaldehyde apparently changes the molecular structure of the starch, removing its gelatinizing properties, so that even when steamed or boiled it still remains a free-flowing dusting powder. When introduced into body tissues it is absorbed and does not produce a foreign body granuloma. Gottschalk[12] undertook an investigation to determine whether this substance was primarily irritating or capable of producing a contact dermatitis. Two hundred and eight volunteers were patch-tested with the material. There were no positive reactions. Ten to fourteen days later the entire group was retested. One positive reaction was obtained. This subject was shown to have a formaldehyde sensitivity. However, on a third test with formaldehyde-treated starch no reaction was noted. Eiseman et al[9] are of the opinion that the formaldehyde starch is somewhat unstable and, on aging, seems to split up, liberating free aldehyde which may act as an irritant to the hands of the surgeon. They reported that one of their resident surgeons developed an irritation of the hands from an aldehyde-treated starch.

Mumford and Auckland[23] reported the case of a patient who showed recurrent congestion, erythema, and irritation on the cheeks and eyelids over a two-year period. Investigation revealed that the odor of burnt coal gas was discernible at the patient's place of employment, and that attacks invariably occurred within twelve hours after a day when the odor was strong. This patient showed a positive patch reaction to formaldehyde. It was concluded that minute traces of aldehydes in the burnt coal gas were responsible for his illness.

Soap and Cosmetics.—Lane and Blank[17] have shown that among the sodium salts of the fatty acids commonly contained in soaps (lauric, myristic, palmitic, and oleic), only sodium stearate and sodium palmitate elicit a relatively low percentage of positive reactions on patch tests. Stearic acid and palmitic acid usually produce no reaction on patch test in the presence of a buffer solution of pH 9. They also demonstrated that highly sulfated oleic acid (sulfato-octodecanoic acid) is usually innocuous on patch testing. It is, therefore, not surprising that these investigators found that a solid lathering cake detergent made primarily from stearic, palmitic, and sulfato-octodecanoic acids and containing little or no lauric acid or oleic acid was non-irritating to the skin both by patch tests and by clinical investigations. Such a product is commercially available as Dermolate.

Sharlit[33] has pointed out that the acid character of the cutaneous surface has led to the opinion that the regular application of alkaline substances to the skin may be responsible for the production of a dermatitis or the maintenance of it. Soap has been so incriminated, but the author is not convinced that the alkalinity *per se* of toilet soap is dangerous. In proof of his point, Sharlit demonstrated that eighteen random commercial face powders all gave alkaline reactions. This appears to be ample evidence, in view of the widespread use of face powder, that the skin tolerates habitual exposure to moderate degrees of alkalinity.

The problem of eczematous sensitization to hair dye is important because of the increasing use of these agents. The so-called penetrating dyes obtained from coal tar are the most efficient, but they are also most likely to produce irritation. Lawrence[18] has reported six cases of dermatitis following the use of paratoluylenediamine hair dye. The eruption was usually noted after repeated exposure. Other related dyes containing para- or meta-phenylenediamine are also commonly used. In the general population idiosyncrasy toward these chemicals is about 4 per cent.[1] Dermatitis from cold wave solutions is well known. A discussion of the chemicals and gums used in cold waving, along with a description of the procedure, has recently been published again.[26]

Zakon et al[57] believes that cheilitis from lipstick is more frequent than is generally realized. These authors claim that the bromfluorescein dyes which are used in lipsticks are more frequently the cause of cheilitis in women than any other factor. Lipstick dermatitis is characterized by swelling and edema of both lips. Scaling, fissuring, superficial erosions, and occasionally small grouped vesicles may be present. In thirty-two cases of lipstick dermatitis, treatment consisted simply of eliminating lipstick containing bromfluorescein dyes.

Cross-Sensitization.—Since R. L. Mayer's original work on cross-sensitization there have been many contributions to the subject. A brief summary is herewith given of those which appeared within the scope of this review. One of Lawrence's patients with a dermatitis due to paratoluylenediamine hair dye reacted to patch tests with that substance and also showed a severe reaction to paraphenylenediamine.[18] In

thirteen cases of allergic eczematous contact-type dermatitis due to nylon stockings, Dokkevitch and Baer[7] showed that azo dyes were responsible, and they were able to demonstrate a cross-sensitization with paraphenylenediamine. Likewise in five subjects with known sensitivity to paraphenylenediamine, they were able to demonstrate cross-hypersensitivity to the azo dyes of the nylon stockings in three. Cornbleet[5] was not able to demonstrate any cross-sensitization to a number of compounds partially related to BAL. However, it is possible that substances with chemical structures more closely allied to the BAL molecule would have yielded more information.

The essential allergen in oil of citronella was found by Keil[15] to be citronellal, an aliphatic aldehyde with one double bond. Patients sensitive to this substance demonstrated cross-reactivity to other essential oils of the same family such as lemongrass and even to other essential oils derived from plants of unrelated botanical origin.

In following up the work within recent years of Rothman and his co-workers and of Rostenberg and Kanof, Strauss[35] reported two cases in each of which the patient had an acquired sensitivity to one of a group of local anesthetics in which each compound consisted of a para-amino benzoic acid ester with a secondary or tertiary amine in the side chain. In one patient sensitivity (as manifested by patch testing) extended to the entire group of related compounds, while in the other there was no evidence (clinically or on patch testing) of any cross-sensitivity to others of the group. Strauss believes that sensitization to an entire group of structurally related compounds may occur as a result of exposure to one of the group, but this does not necessarily occur. Whether or not group sensitization has occurred must still be determined by patch testing or clinical trial in each individual case. Sulzberger et al[40] demonstrated that only 10 per cent of patients who developed a dermatitis from a sulfonamide ointment showed a positive patch reaction exclusively to that sulfonamide. In 90 per cent there was evidence of cross sensitization to other sulfonamides and to chemical radicals and substances related to sulfonamides.

Rhus Dermatitis.—The magnitude of the public health problem created by Rhus poisoning has been stressed by Turner[43] while calling attention to the inadequacy of preventive measures now available. The two new chemical herbicides, ammonium sulfamate and 2,4-dichlorophenoxyacetic acid (2,4-D) provide the first really promising solution to this problem.

Templeton et al[42] made studies on the hematologic, urinary, and temperature changes occurring during poison oak dermatitis. It was found that 80 per cent of the patients showed moderate temperature elevations, usually not above 100° F. Fifty per cent developed milk leukocytosis, and about the same percentage also showed a mild degree of eosinophilia. No urinary changes were noted.

Stratton[34] administered three different poison oak antigens orally or parenterally to determine their effectiveness both in prophylaxis and therapy. He found that the antigen containing lobinol, the vesicant fraction, was an efficient oral prophylactic but was less effective parenterally. The antigen containing all the fractions except the vesicant proved to be the best parenteral agent from the standpoint of prophylaxis and treatment. However, while these extracts are of value in prevention, it is now generally realized that their use in treating the acute phase of toxicodendron dermatitis is inadvisable.[27]

Klasson[16] has used ascorbic acid in the treatment of poison oak dermatitis with success. The rationale behind this form of therapy is this: It is assumed that lobinol decomposes the protein molecules of the cutaneous tissues to alkyl amines, of which histamine is one. Histamine at first produces an increased arterial pressure by direct action on the arterial wall, but ultimately increased capillary permeability results. Ascorbic acid is known to maintain vascular tone, and Klasson assumed it might counteract the toxic action of histamine. In actual practice it was found that ascorbic acid given intramuscularly in a maximum daily dose of 600 mg. definitely reduced the period of treatment. The drug may also be used orally in prophylaxis.

Robinson[29] found that the use of refrigerants, especially ethyl chloride, in Rhus dermatitis relieved pruritus early and considerably shortened the duration of the disease.

Witherspoon[45] has recommended a sodium perborate cream as a simple, efficient, and acceptable remedy for Rhus dermatitis. Nascent oxygen is released gradually and is assumed to detoxify the resins remaining on the skin.

Another warning against the use of solutions of iron salts in poison ivy dermatitis has been sounded by Strauss.[36] It has been known for some time that

solutions of ferrous sulfate or ferric chloride may leave residual pigmentation at the site of the dermatitis. In Strauss' patient such pigmentation slowly disappeared over a six-year period.

Miscellaneous.—Carpenter[4] has reported four cases of contact dermatitis which were followed within two to ten days by an erythema multiforme-like eruption. The author believed these sequelae were produced by the absorbed bacteria, viruses or their products from the superficially infected areas of the dermatitis venenata. In a study on pyrethrum dermatitis, Lord and Johnson[19] found that the dermatitis-producing factor is a distinct component of the pyrethrum flower and may be separated from the pyrethrin content. Ellis[10] has demonstrated that the thiosalicylic acid radical is the usual sensitizing factor in Merthiolate sensitivity. Pirila[25] reported six cases of sweat band dermatitis due to Thiocol (or Thioprene). Nine patients who were sensitive to an oxycholesterol-petrolatum ointment base (Aquaphor) were reported by Ellis.[11]

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Industrial Dermatitis

The essential principles in the diagnosis, treatment, and prevention of industrial dermatitis have been reviewed by Downing,[2] Tolmach,[19] and Macaulay.[8] Downing[2] pointed out that the largest group with occupational dermatoses consists of housewives whose dermatoses are a result of exposure to soap, soap powders, squeezing oranges, handling raw fruit and vegetables, et cetera. In regard to the industrial commissioners, Downing expressed appreciation of their humane attitude: "These officials are admittedly slightly partial to the employe, and perhaps justly so. To the insurer and its representatives, either lawyers or physicians, it is just another case, the loss of which will not in any way change their routine. To the injured worker it is a tragic, all-absorbing controversy, the solution of which may determine his future and that of his family."

Tolmach[19] believes that the incidence of sensitization dermatitis in industry as a whole is actually less than the generally estimated 20 per cent. Furthermore, he is of the opinion that the atopic individual is not more easily sensitized in industry than so-called "normal" people. Downing, in an editorial comment,[3] disagreed. In his experience he found that atopic individuals should not work where they will contact sensitizing chemicals, especially where there is exposure to irritating dust, fumes, or soap mixtures. The reviewers are of the same opinion.

A number of reports on dermatitis in diverse and specialized industries have been published within the scope of this review. Samitz[13] found that a negligible number of dermatological cases occur in the poultry industry. There are two reasons for this: (1) The process of slaughtering and cleaning the fowl does not require the use of any chemical agent, and (2) protective clothing prevents dermatitides due to physical agents, such as friction or cold. Samitz and Gibson[14] found that longshoremen and harbor workers likewise have a low incidence of occupational skin disease. Among 10,700 case histories of illnesses and accidents reviewed, only 385 (3.5 per cent) had skin diseases. Parker[10] has mentioned some of the difficulties in the diagnosis and management of dermatitis in the shoe industry. Pirilä[11] completed an extensive study on occupational diseases of the skin among paint factory workers, painters, polishers, and varnishers in Finland. A total of 1,142 paint factory workers, white lead workers, and painters was studied. Of these, 119 had had an occupational dermatosis or developed an occupational dermatosis during the course of the study. The paint factory workers were divided into three groups: (1) paint workers, of whom 20 per cent developed a dermatosis, (2) washers and charwomen, who showed a 67 per cent incidence of occupational dermatoses, and (3) outdoor workers and office employes, with only 1 per cent occupational dermatoses. Not a single white lead plant worker showed any evidence of an occupational dermatosis. Ten per cent of the painters had or had had an occupational dermatosis. Toxic dermatitis and allergic eczema were the most common manifestations of the dermatoses. In 96 per cent of the cases, the dermatosis had begun on the hands and arms; in the remaining 4 per cent, the face was first involved. There were eruptions on the trunk in only 10 per cent of the cases. Finnish sulfate and kiln turpentines were the main causes of the dermatoses. Thirty-one per cent of the total were considered allergic (sensitization) reactions; 69 per cent were considered toxic (primary irritant) reactions. Hypersensitivity could be demonstrated in only 28 per cent of the cases. The greater incidence of allergic reactions was undoubtedly due to the fact that turpentine, a strong sensitizer, was used in great abundance in the occupations presented. Disability was caused in over 50 per cent of the cases. The allergic cases were

the most severe, were generally of longer duration, caused disability more frequently and for a longer time and compelled the workers to change occupation oftener than toxic dermatitis. Of persons engaged in the same work, a greater number of women were found to have had occupational dermatoses than of the men. Thus, in the paint factories, 30 per cent of the women but only 15 per cent of the men had acquired dermatoses.

Kilpinen[5] conducted a mass survey to determine the incidence of occupational eczema among bakers in Helsingfors. Only eight cases of occupational eczema were found in 653 bakers examined.

An exhaustive study on the correlation of the boiling ranges of some petroleum solvents with irritant action on the skin was completed by Klauder and Brill.[6] It is known that petroleum is composed of an intimate mixture of thousands of hydrocarbon compounds with paraffins (C_nH_{2n+2}) and cycloparaffins or naphthenes (C_nH_{2n}) predominating. Oleofins, acetylenes, aromatics and other cyclic hydrocarbons are present in lesser amounts. The primary separation of petrolatum into its commercial products is accomplished by means of distillation. As a general rule, the more volatile fractions (boiling ranges below 450° F.) are all primary cutaneous irritants and exert a defatting action on the skin. A solvent with a boiling range of kerosene or lower will uniformly give positive reactions on patch testing. The more viscous fractions (boiling ranges above 600° F.) exert no irritant action. To reduce the hazard of dermatitis from petroleum solvents, these investigators suggest the use of a solvent for a particular job with as high a boiling range as is consistent with the purpose for which it is to be used. In jobs where kerosene is used, that of paraffinic origin should be preferred to one of naphthenic origin because the latter is more irritating. Klauder and Brill found that the cutaneous reaction to petroleum oils with boiling ranges intermediate between kerosene and the viscous lubricants varied considerably in normal persons from no reaction to varying degrees of positive reactions. The skin of negroes showed a high degree of tolerance. There was a lessened degree of tolerance of the skin of workers with dermatitis caused by solvents and of patients with dermatitis not caused by solvents. These co-workers devised a test to determine the individual tolerance to petroleum oils and solvents. Ten distillation fractions with different boiling ranges extending from that of kerosene to that of light spindle oil are used. This report should be read in its entirety by those physicians concerned with the petroleum industry or its by-products.

The chlorinated hydrocarbon solvents are high on the list of efficient degreasers. One of these, Permachlor (or trichlorethylene) is commonly used to degrease automobile motor parts. Contact with the skin produces a dry, cracking dermatitis. Safety procedures for those using this solvent have been outlined by Krieger.[7] Casite (a naphtha derivative) is similarly used to remove sludge from motors. It may also produce a dermatitis following skin contact.[12]

McKinley[9] had reviewed the dermatological hazards of the plastic industry. The term plastics is applied to synthetic resins. These range from solid molded materials, such as telephone receivers, to flexible sheeting, such as raincoats, shower curtains, et cetera. As a rule, the finished plastic is inert, but the chemicals used in making it may be harmful, e.g., formaldehyde. Materials known as plasticizers are added to plastics to reduce the brittleness of the plastic. These are natural gums, glycol derivatives, et cetera, and may produce a dermatitis. Stabilizers and antioxidants prolong the life of plastics by protecting them against the effects of light and heat. They include organic and metallic radicles, some of which are primary irritants. Hardeners aid in setting some resins. Hexamethylenetetramine (Hexa) is most frequently used and is a well-known sensitizer. The control of these hazards devolves upon proper ventilation, good housekeeping, showers for the employes, and frequent changes of work clothing.

Erwin[4] reported on skin irritations from fiberglas plastics. In most plastics the resins are of primary importance, and the filler is of secondary importance. However, in fiberglas plastic, the glass filler is the primary element. The small particles of glass are mechanical irritants and in some instances appear to be actual sensitizers. With continued employment, most workers become "hardened." However, some require transfer to new jobs. Proper clothing, protective sleeves, adequate washing, moistening of the material before it is machined or cut, and protective creams are among the necessary preventive measures. Samitz[14] reported three cases of fiberglas dermatitis occurring in workers repairing the insulation on refrigerators. Schwartz,[16] while investigating an outbreak of dermatitis from women's suits and children's coats, found that fiberglas was used as a lining for this apparel. Similar dermatitis had appeared among the girls working on the linings in the factory. Manufacturers have been advised against the use of this material in clothing.

The occupational pigmentary changes which may occur in the skin have been

reviewed by Schwartz.[17] These may consist of an excess of melanin or melanois, deposits of metallic substances in the skin (tattooing), and dyeing of the skin either from external application of the dye or deposition of the dye in the skin after ingestion. The occupational causes of excessive formation of pigment in the skin are (1) excessive exposure to sunlight or actinic rays, (2) exposure to coal tar, (3) exposure to crude petrolatum and residuals of petrolatum distillation and "cracking," and (4) exposure to asphalt. Photosensitization may develop from the last three substances named and also from exposure or ingestion of certain plants. As a result of photosensitization, protective pigmentation develops. Monobenzyl ether of hydroquinone, used as an antioxidant in rubber gloves, is the only substance known which produces an occupational depigmentation of the skin without causing a dermatitis. Apparently this compound is dissolved out of the gloves by the perspiration and absorbed into the skin where it prevents the combination of oxidase with the pigment precursor. The fact that repigmentation takes place after exposure is stopped indicates that the chromoblasts are not destroyed.

Many types of seeds are treated with organic mercury compounds to kill fungi and prevent seed rotting. Ethyl mercury phosphate or chloride, or hydroxymercuric compounds are most frequently used. Schulte[15] has indicated that in the actual operation of mixing this material with the seeds very few cases of dermatitis are encountered.

The importance of recognizing ragweed dermatitis when it occurs in industry is stressed by Slater et al.[18] If contact with ragweed is not incident to the occupation, this type of dermatitis is not compensible. The authors reported two such cases in industrial workers where their jobs, although suspected, were actually not the cause of their dermatitis.

Campbell and Schwartz[1] have recorded two unusual outbreaks of occupational dermatitis. Two situations were described where irritant fumes, carried in the natural flow of air from cool to warmer atmospheres, produced dermatitis in workers engaged in innocuous tasks at distant parts of large workrooms.

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Microbic Eczemas (Bacterial, Mycotic)

Dermatitis of the external auditory canal frequently is a troublesome disorder. Etiologically, this is not an entity. Many different factors or combination of factors may be responsible. The role of fungi has been overplayed. Pathogenic fungi may be found, but rarely. Where molds are present, they are frequently secondary invaders. Infection and infectious bacterial eczemas are rather frequent, although they may also be superimposed on other forms of eczema, especially seborrheic dermatitis and localized atopic dermatitis of the ears. Pseudomonas aeruginosa (bacillus pyocyaneous) was cultured by Callaway[1] in a case of an acute eczematoid dermatitis of the canal and pinna of the ear of a man fifty-one years of age. Routine antiseptic measures, including local and parenteral use of penicillin, failed. An aqueous solution of streptomycin containing 2,500 units per c.c. produced a rapid cure.

According to Eva Schwarz,[9] skin diphtheria often presents the picture of eczematoid or intertriginous lesions; usually it is located in the folds behind the ears, spreading from there to adjacent parts of the neck and the hairy scalp. In all twenty-four patients seen by her, the area of the ear and the scalp were affected; in nine of them there were also eruptions on the trunk and limbs. The lesions are chronic and resist the usual treatment of eczema. Mostly children, but also adults, are affected. Usually the course of the affection is benign and the general condition of the patient remains undisturbed. However, this is not always so, especially in the deeper types; even in the superficial type, there have been some cases with fatal outcome.

The treatment consisted of intensive local treatment with disinfectants such as wet applications with rivanol 1:1000, pantosept 1:1000, or Eau d'Alibour. After the regression of the acute symptoms, bandages were applied with 1 per cent rivanol vaseline, or a combination of 1 per cent rivanol and 3 per cent salicylic acid in vaseline. Later Arning's tincture (Tumenol-Ammon. 8.0, Anthrarobin 2.0, Tinct. benzoes 30.0, Ether 20.0) and Lassar's paste were used. In most cases, clinical improvement and negative smears followed this simple treatment in one or two weeks. In some instances there were recurrences and the illness lasted several months. Patients with diphtheria of the skin should be isolated because they may become the source of infection in others.

Desaux and his co-workers[3] report about twenty cases of different dermatoses where they have found proteus vulgaris. They found the proteus bacillus especially in eczema around the anus, with and without secondary allergic eczematization; furthermore in intertrigo. They believe that proteus also plays a role in the etiology of certain cases of vulvovaginitis and balanitis. They also have found proteus bacillus in cases of paronychia, varicose ulcer and other conditions.

Furthermore, they observed a patient with an erythematous dermatitis of the neck where they could demonstrate the presence of proteus in the stools besides enterococci, E. coli and staphylococcus. As far as treatment is concerned, proteus vulgaris in superficial dermatoses seems rather easily destroyed by the common antiseptics. When the dermatitis involves the deeper layers of the skin, surface disinfection is not sufficient; the authors recommend x-ray treatments. The allergic dermatoses due to proteus are helped by intradermal injections of an autogenous vaccine, which must be used prudently. One must be guided by the local, focal and general reactions, which are by no means rare.

Frequently they have observed positive intradermal reactions when injecting a suspension containing from 25 to 50 million germs. These were characterized both by immediate urticarial responses as well as delayed reactions after twenty-four and forty-eight hours which were sometimes painful. Although the proteus was frequently associated with other germs, especially staphylococci and Escherichia coli, the authors accord the proteus an etiologic role, because it is found only at the site of the dermatosis and possesses antigenic capacity.

Another case of eczema attributed to infection with the proteus bacillus is reported by Fejer.[5] The patient suffered from a generalized eczema of ten years' duration. There was an eosinophilia of 26 per cent, toxic changes in the bone marrow, a pathologic electrocardiogram and albuminuria. There existed a congenital phimosis. From the preputial sac came a purulent discharge, containing bacillus proteus. Autovaccine gave a positive cutaneous reaction. After circumcision the eczema and the general toxic condition cleared up within two weeks. Fejer considers this case an example when a microbic focus of the skin originated severe dermal and internal trouble. The role of focal infection in dermatologic disorders is a matter of controversy at present. Epstein[4] feels that focal infection plays a much greater part than is generally realized. He reports two cases of a persistent localized bullous eruption which resisted anti-infectious external and internal treatment, but cleared up rapidly and permanently after the removal of infected teeth.

An interesting study regarding the relationship of intradermal reactions of the delayed type to the absorptive behavior of the skin, is presented by Seeberg.[10] His investigations were prompted by several observations. It is known that the tuberculin reaction may vary in strength temporarily; it is also known that the response to tuberculin can be more or less attenuated for longer or shorter periods. A transient decrease in the activity may be seen, for instance, after exposure to sunlight. Examining subjects with erythroderma, Seeberg found the disappearance time of a wheal to be very short; also the disappearance time of a tuberculin wheal was extremely short; the tuberculin failed to produce any reaction whatsoever. Seeberg presumed that this tuberculin anergy was due to changes in the absorptive capacity of the skin, leading to a rapid absorption. Seeberg used intradermal tests of the delayed type for his studies, among them tuberculin test, trichophytin test,

streptococcic suspensions. Both absorption and reaction studies were carried out in different states of the skin, and compared with each other; for instance, normal skin, skin exposed to sunlight, to mercury arc light, skin frozen with carbon dioxide, urticarial skin, edematous skin and skin changed by eczema and erythroderma. These studies showed that the absorption in normal skin is slower than that in skin exposed to the mercury arc light; slower in less-pronounced edematous skin than in more edematous skin; and slower in less-severe eczematous skin than in the more-severe eczematous stage. Experiments with tuberculin-type reactions clearly showed the significance of the absorption time. With rapid absorption there was no reaction or only a slight one. With prolonged absorption there were reactions of varying intensity. This applied both to allergic reactions, such as the tuberculin test, and toxic reactions, such as the Schick test. There were however some "paradoxical" reactions. Some of the absorption studies were carried out with radioactive phosphorus, P. 32.

Seborrheic Dermatitis

There is no agreement as yet among the dermatologists as to what and what not belongs to seborrheic dermatitis. What now is commonly called seborrheic dermatitis consists of a group of eczematoid eruptions. According to Darier,[2] they present the following four characteristics: (1) the lesions are usually dry, (2) they are sharply outlined, round, or polycyclic, (3) they persist long without a change of the clinical picture, and (4) their cure is easily accomplished by certain topical medications.

Jadassohn[6] stresses the following points as a distinction of seborrheic dermatitis from other eczematoid eruptions: The lesions of this dermatosis are very superficial, hardly elevated. The color most frequently varies from a pale red to a yellowish red. The scales are often of a fatty consistency; there is an outspoken tendency to peripheral growth, and often to central healing. In its pure form, seborrheic dermatitis does not present vesicles or oozing.

This typical picture of seborrheic dermatitis is seen not infrequently on the chest and back of the adults and in children. This form is recognized by everybody as belonging to seborrheic dermatitis. The etiology is unknown, but a microbic causation is assumed by many students. However, a special disposition for this disease is an important factor in its causation—a disposition which seems to be hereditary.

References to seborrheic dermatitis in the literature by no means always refer to this typical uncomplicated picture. Combinations and transitions to other forms of eczema are quite frequently found. Intertriginous dermatitis may be combined with this condition. As a whole, American literature tries to use the term seborrheic dermatitis in the more restricted sense. In the European literature, especially the British school, the term seborrheic eczema covers a wider field.

According to Lane and Crawford,[7] there is in seborrheic dermatitis an alteration of the function of the sebaceous glands in some individuals that leads to a so-called "seborrheic diathesis." There is hyperactivity of the sebaceous apparatus, which is sensitive to many stimuli and easily touched off into an inflammatory eruption that may appear in widespread and distressing fashion. The constitutional background obviously cannot be changed. It may be first manifested at adolescence, but endocrine therapy is fruitless. Infectious factors have not proved important, but secondary infection may be quite a problem. An environmental influence may affect some cases. Dietary approach gives inconstant results; some patients do better with a low fat intake, and others may benefit more from a restriction of carbohydrates. Large amounts of the B complex seem to help an occasional case, as do also injections of crude liver extract. No systemic approach seems to be of outstanding value.

Midana[8] reports the "coprologic" picture of seborrheic dermatitis of babies and children between the ages of eight months and six years (thirty patients). From the stools he studied the enzymatic activity of lipase, trypsin, amylase, and erepsin without finding any noteworthy changes compared with normals. A slight diminution of the activity of trypsin and increase of erepsin is explained by him by the increased speed of the intestinal passage so often found in tiny patients with seborrheic dermatitis. Inasmuch as he did not find an organic basis for the gastrointestinal disturbances, the author believes that they are an expression of a functional alteration, in the sense of a vagotonic reaction. The psychologic aspects of seborrheic dermatitis were studied by Wittkower[11] on 100 unselected cases of British military personnel. The patients revealed themselves as somewhat unsociable, shy and afraid of persons in authority. Lack of self-confidence with feelings of inferiority and insecurity caused them much anxiety at their jobs. They suffer from worries and unreasonable fears. Thirty to 40 per cent had nervous habits, such as nail

biting or stammering; sixteen suffered from gross psychological disorders. In seventy-six of the 100 patients the onset of their skin trouble was preceded by some rather severe psychologic trauma that affected either the patient's social status or self-esteem. Wittkower stresses the point that the personality type described is very common and not specific for seborrheic dermatitis. Furthermore, only two-thirds of the patients studied conformed to it. However a comparative analysis of some striking characteristics of this personality type revealed that they were found much more frequently among patients with seborrheic dermatitis than in a control group.

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Miscellaneous Eczemas

Nummular eczema is discussed by Van Studdiford, McLean and Alvarado.[11] The term was coined by the French dermatologist, Devergie, to describe round patches of dermatitis which develop mainly on the extremities, especially the upper one. It is accompanied by redness, vesiculation, itching and a serous secretion. This is a rather common dermatologic condition. Van Studdiford and his co-workers[11] believe that the following are associated with the development of nummular eczema: (1) a hyperactive personality with nervous instability, (2) occurrence during the phase of diminishing gonadal activity, (3) a precipitating emotional problem, (4) a preceding minor skin disturbance which fixes the attention of the personality on the skin. These authors recommend particularly the use of pyridoxine hydrochloride. Allison[1] claims that these patients will improve with injections of liver extract and vitamin B complex; the reviewer[5] has the same impression, although it is difficult to establish definitely the value of such therapy in clinical trials. One might mention, however, the fact that Sullivan[10] demonstrated the role of the vitamin B complex, other than thiamine, in regard to cutaneous injuries in rats. The extent of such injuries is increased and healing is delayed where such deficiency existed.

Engman[4] is not prepared to accept a nervous etiology. He believes the etiology of nummular eczema is entirely unknown. The role of focal infection in this condition is considered only secondary by Van Studdiford and co-workers, but more important by other authors.

Carpenter, Nuckolls and Dyke[2] studied nineteen cases of nummular eczema among Navy personnel in regard to focal infection. Prostatitis was found in nine, dental infection in three, and upper respiratory foci in seven. Intramuscular injections of penicillin with gradually increasing doses from 2,000 to 15,000 units produced immediate improvement of the skin lesions, and also of the prostatitis Two patients experienced Herxheimer-like local flare-ups.

Another stubborn eczematoid eruption of unknown etiology is the so-called exudative chronic discoid and lichenoid dermatitis or Sulzberger-Garbe disease. This is a rather rare entity. Kocsard[8] reports three cases; the neuropathic element was evident; two patients were cured with injections of large doses of sodium arsenate. Exfoliative dermatitis, its classification, diagnosis and treatment, is discussed by Kierland.[7] It should be considered a symptom complex. Exfoliative dermatitis may represent a reflection on the skin of serious systemic disease, may be an extension of a pre-existing skin disease such as psoriasis or seborrheic dermatitis, or may arise from purely local conditions, such as contact dermatitis or drug eruption. The most common complication is secondary infection of the skin. Pneumonia and hypoproteinemia are frequently encountered. Treatment is symptomatic while

a search is made for the etiologic factor. A nutritious, high protein diet should be provided; vitamins and blood transfusions are given where indicated. BAL should be given to all patients whose dermatitis is due to arsenic. Langley and Morgan[9] found chloresium (watersoluble chlorophyll in a hydrophilic ointment base) very effective in two cases of exfoliative dermatitis.

Eichenlaub and Osbourn[3] studied the role of the liver in congestive eczema. The commonest form is varicose eczema. Patchy eczema, usually of the legs, sometimes of the arms and trunk, was also classified in this group. (This condition probably corresponds to nummular eczema.) A series of eight such cases with disturbed hepatic function is reported by these authors. Füsthy and Pastinszky[5] studied the Weltmann reaction in various dermatoses, including eczemas, and consider it an exact control for disturbances of the liver.

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Pruritus Ani et Vulvae

Pruritus of the anus and vulva is a symptom. Perhaps no other eczema, except eczema of the hands, is due more to multiple causation and a variety of factors, than this condition. To the dermatologist, pruritus ani includes only those cases where there is itching without noticeable pathologic changes of the skin. In the general literature, however, the term includes all the itching eczematoid conditions of the anal region. No wonder that there is such a divergence of opinion regarding the etiology and therapy of this condition, because actually we are dealing with different entities. Atopic dermatitis, contact dermatitis, fungus infections and bacterial eczemas and their combinations, together with additional factors may be responsible. Swinton[5] discusses the factors that may give rise to anal itching or may cause an anal pruritus to become a definite and intractable pathologic entity and presents the methods of treatment that have proved most satisfactory in his hands.

Nearly all cases of pruritus ani are precipitated by some local mechanical factor. Anal pruritus is often initiated by a precipitating factor such as diarrhea or constipation, following which, scratching may cause local congestion, irritation, trauma and infection. This in turn causes more itching and establishes a scratch-itch cycle. The importance of avoiding irritation cannot be overemphasized. However, a wide range of factors may be responsible for the development of pruritus ani. Among the physiologic factors, Swinton mentions the irritation from soap and the sulfite in certain toilet tissues. Excessive intake of carbohydrates and fruit juices predisposed to an increased alkalinity of the affected parts. The incidence of fungous infections was not high. Pyogenic flora, with occasional streptococci, was usually found. An allergic background was encountered in a few patients. Phenolphthalein from laxatives may cause local sensitization and pruritus ani. Psychogenic factors should not be overlooked. Nervous tension, fatigue, worry, maladjustments and frustrations are frequently observed. Sexual problems may enter into many of these cases. Small amounts of tincture of belladonna with luminal is a helpful sedative. Normal bowel functions should be established. Intake of carbohydrates, roughage and alcohol should probably be reduced. Roentgen therapy is rarely used at the present time. The presence of specific dermatologic skin conditions should not be overlooked.

In certain stubborn cases search for food allergies may be necessary. Too much attention has been given to local therapy. Adequate local hygiene is important. The anal region should be cleansed routinely with cotton moistened in warm water. Toilet paper and soap are forbidden. Sitz baths in potassium permanganate

solution for fifteen to twenty minutes are used almost routinely, followed in mild cases by the application of calamine lotion with 1 per cent phenol. In severe cases continuous wet dressings and hospitalization may be necessary. In general, bland solutions are used and ointments avoided. For lubrication, castor oil or olive oil may be used sparingly. Ammoniated mercury ointment or 2 per cent silver nitrate solution may help when fissures develop. Coal tar preparations are indicated at times. Surgery has been used less and less. It is indicated for the removal of sources of infection and correction of local disease, such as infected crypts, contracted anal canal, large skin tabs, anal fissures and fistulas. Alcohol injections gave temporary relief, and permanent relief in a high percentage treated with the Buie technique. However, the resulting sloughing and excessive scarring was not desirable. Alcohol injections and other radical procedures should be reserved for the severe cases. There will be a high incidence of recurrence following surgery if adequate attention is not given to the various etiologic factors.

Aldrich[1] believes that a fungus infection is the most common, if not the only direct cause of anal and perianal itching. However, it is considered advisable to bear in mind the predisposing and the indirect causes as well as any aggravating factors before directing attention to the local treatment. Aldrich used a 2 per cent emulsion of undecylenic acid in the treatment of fifty-four cases of pruritus ani and pruritus vulvae or both. The emulsion was applied both in the morning and at night. Fifty cases were greatly improved or cured.

Local treatment of pruritus ani with aluminum hydroxide gel is recommended by Friedman et al.[3] The management of pruritus ani in the armed forces is described by Marks.[4] Clarke[2] presents a case of pruritus vulvae, due to a rubber condom. From his experiments it became apparent that the irritation was due to the presence of alkali from the potassium oleate. The patient gave positive patch test reactions to caustic soda in a concentration as low as 0.05 per cent. Inasmuch as the sensitivity in this case was about sixty times that of the normal skin, the action of alkali on this woman's skin appears to be that of allergic sensitization rather than simple chemical damage.

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Urticaria

The etiologic approach to chronic urticaria and angioneurotic edema is presented by Lieder and Pennock.[5] For an etiologic diagnosis, the first essential is a careful, painstaking, chronologic history. Attempts must be made to determine not only the specific causes, such as foods or drugs, but also the influence of emotional factors. Food factors are determined best by placing the patient on an elimination diet. During this period of elimination diet, a careful investigation should be made for possible foci of infection or infestation. Even though the most important foci of infection seem to be in the teeth, the tonsils, nasal accessory sinuses, gall bladder, prostate, cervix, appendix, and colon should be investigated. There should be stool examinations for parasites and ova. Intradermal skin tests are usually of little value. Occasionally inhalants are factors and their avoidance may aid in the treatment. The authors stress drug and bacterial allergy as being the most important etiological factors. Food allergy is a factor in the acute urticarias more than in the chronic types. According to Kelley,[4] there is often a multiplicity of causes in urticaria such as food, foci of infection, bacteria and psychogenic disturbances. He considers epinephrine and ephedrine the classical therapeutic agents. Also recommended by him are calcium, synthetic vitamin K, and splenic extracts. Autogenous or stock vaccines from nasopharyngeal or stool flora occasionally may afford relief. Successful treatment of an urticaria caused by wheat bread is reported by Stauffer.[9] The patient was treated with increasing intradermal injections of an extract made from her bread. Kaywin[3] points out the following six factors as possible aids in the recognition and evaluation of the role of emotional disturbances in urticaria: (1) a life situation for the period preceding the onset which is generally unhappy and anxiety-provoking; (2) sudden onset of symptoms, which has as its precipitating factor some frustrating experience; (3) a lack of an allergic history or manifestations; (4) presence of subjective and objective signs of

anxiety; (5) chronicity of symptoms; (6) a personality type characterized by shyness, easy embarrassment, blushing and immaturity with a tendency toward exhibitionism.

Menstrual urticaria has long been known to be an allergic phenomenon.[10] Under the title, "Erythema urticatum premenstruale," Maruri and Zorrilla[6] describe an erythemato-urticarial patch eruption of the hands of a young woman. The eruption always originated a few days before the onset of the menses and lasted twenty-three days. After intracutaneous injections of estradiol benzoate and progesterone, the lesions lasted six days only. Pumar[8] reports seven cases wherein the urticaria was completely cured by a treatment with quinine and metaquin. The author emphasized the outspoken character of the urticaria and its close parallelism with malaria; in nearly every instance the skin manifestations appeared with the period of hyperthermia and receded following the crisis. In all cases the urticarial attacks disappeared, coincident with the other symptoms, with the antimalarial treatment. For this reason one may consider the urticaria to be a manifestation of the malaria.

Katzenellenbogen studied eighty cases of acarodermatitis urticardoides, a disease which is endemic in Palestine. The eruption is found in farmers, porters, drivers, milkers and stablehands and is caused by the mite Pediculoides ventricosus. The mites live in straw and grass, with the latter being the main source of the infestation. The forearms, neck and trunk were the parts most frequently affected, the legs rarely and only when the grass came into direct contact with the skin. The rash appeared as discrete papular lesions, lentil to bean sized, with urticarial wheals partly surmounted by tiny vesicles. The eruption lasted from six to ten days. Acarodermatitis appears in June and July and September and October. Fahleh grass which became infested with the mites was held responsible. The disappearance of the mites in the grass coincided with the disappearance of new cases of acarodermatitis urticarioides. Insects, such as mosquitoes, bedbugs and lice, may produce urticaria. Mellanby[7] demonstrated that the urticarial response to mosquitoes is an acquired allergic reaction. He exposed, at different periods, twenty-five volunteers who had never travelled outside Britain to the bites of Aedes aegypti and Anopheles maculipennis atroparvus. All patients showed similar reactions and no itching, but a delayed reaction occurred usually between twenty to twenty-four hours in the form of a red patch of 3 cm. in diameter, surrounding the bite, with a definite central papule. The itching lasted for several days. On the repetition of the biting by A. aegypti, the reaction was quite different. An urticarial reaction, highly pruriginous in nature immediately developed. This local reaction disappeared within two hours, but the delayed reaction regularly ensued. After further exposure these reactions were modified by the diminution and even disappearance of the delayed reaction. In some cases repeatedly exposed to thousands of bites by A. aegypti, it was observed that the immediate reaction also disappeared. The author suggests that these reactions are distinct and possibly caused by different antigens in the mosquitoe's saliva. It has been suggested that this increased tolerance to the bites of these pests is the result of true immunity. While a true anti-insect immunity has been demonstrated in the case of ticks, no such mechanism has as yet been proven experimentally in regard to mosquitoes. For this reason, Dubin, Reese, and Seamans[1] undertook experiments to see whether rabbits could be protected against mosquitoes by a course of active immunization by means of a suspension and an extract from killed, ground up, normal female mosquitoes. The authors were not able to protect rabbits against mosquitoes with this method. Moreover, the rabbits inoculated with a suspension of the mosquitoes became sensitized to mosquito bites in contrast to the normal nonsensitive rabbits. The sensitized rabbits showed large, indurated reddened papules at the site of the bites. These cutaneous reactions began in about thirty minutes, and reached their maximum size in about five hours. Attempts at desensitization of the sensitive animals were unsuccessful. Passive transfer was negative.

Urticaria from physical causes such as pressure, cold, heat and light will be dealt with in a special review on physical allergy in dermatology.

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Antihistaminics in Dermatology

Experimental Studies

There are contradictory reports about the ability of the antihistaminic drugs to modify or suppress experimentally produced wheals. Nexmand and Sylvest[4] working with lergitin (Antergan) and amidryl (Benadryl) did not observe such an effect. However, they noticed a considerable reduction of the subjective symptoms in these experimentally produced whealing reactions from histamine and others, such as urticarial skin reactions in allergic individuals, Prausnitz-Küstner test, dermographism. In Nilzén's[5] experiments, simultaneous injection of the antihistaminics Antergan and Antistine with atropine, peptone, morphine and histamine produced a mild reduction of the wheal and flare caused by these substances, without the addition of the antihistaminic. Nilzén believes that these experiments support the histamine theory of Lewis. In his opinion the antihistaminics do not neutralize histamine in a chemical sense. Rather they seem to become attached to the cells and make them refractory against histamine. This can be demonstrated on the gut of the guinea pig, which remains refractory against histamine after it has been perfused with antihistaminics, even following several washings.

Borelli[1] studied the effect of the antihistaminic drug Dimetina (dimethyl aminoethyl benzylaniline) upon the ultraviolet reaction of the skin. In the majority of cases a rise of the threshold erythema was noted. Also an increase of the latent period and a diminution of the degree and duration of the erythema. Only occasionally was the pigmentation less severe. However, the subjective symptoms, such as burning and itching, were missing, even if they had been present and were still existing in areas that were irradiated as a control on the preceding day. Borelli concludes from his studies that a great part of the so-called antihistaminic (antiallergic) action of these drugs is due to their anesthetic capacity.

In Olivetti's[6] experience the oral administration of the antihistaminic drug Dimetina did not relieve experimentally produced pruritus, although the same drug was efficacious in relieving the spontaneous pruritus of various dermatoses. Olivetti confirmed also the old observations about the ability of antihistaminic drugs to inhibit the wheal from histamine. More diluted solutions of Dimetina were more efficient in this respect. Intradermal injections of Dimetina as well as Antistin produced a moderate local anesthesia. The anesthetic action of Benadryl was studied by Leavitt and Code.[3] These authors compared the analgesic effect of intracutaneous injections of Benadryl and procaine. Pain thresholds were determined by the use of a simple type of an electric algesimeter. The results were as follows: By means of electric algesimetric determinations, Benadryl in dilutions of 1:500, 1:1000, 1:5,000, 1:10,000 and 1:20,000 was found to possess anesthetic potencies similar to those of procaine in dilutions of 1:200, 1:400, 1:800, 1:1,600 and 1:3,200, respectively.

Dreisbach[2] suggests anesthetic action may be responsible for the relief of subjective symptoms which the antihistaminic agents afford in penicillin reactions. He demonstrated that Benadryl and Pyribenzamine were ineffective in preventing the development of the Arthus type of skin reaction to penicillin in rabbits. However, mixed with histamine, Benadryl or Pyribenzamine prevented the typical skin reactions of histamine. Therefore, this author suggests that the nature of relief obtained with the "antihistaminics" is related to the central and peripheral sensory depression of these agents. Ingestion of the antihistaminic 3015 RP, which is approximately five times as effective at Neoantergan, did not influence the tuberculin reaction in children, according to Wissmer.[7]

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Clinical Observations

The antihistaminic drugs are widely used and abused. As Ratner[39] states, they deserve a place in our armamentarium as symptomatic remedies. In dermatologic allergy, their greatest value lies in the treatment of acute urticaria and drug eruptions and in the relief of itching in a number of cases of dermatoses associated with pruritus. To Benadryl and Pyribenzamine have been added Antistine, Decapryn, Neoantergan, Theophorin and Histadyl and Thenylene, the latter two but different trade names of the same chemical. The availability of a larger number of antihistaminic or antiallergic drugs is a definite advantage for the control of pruritus. Cases that are not helped by one of these compounds may be relieved by another. Where side effects demand discontinuation or reduction of dose, another antihistaminic may be well tolerated. Although they are only symptomatic drugs, the management of the itchy patient has been made much easier since their advent.

Antistine.—Antistine has the advantage that it can also be given intravenously, intramuscularly and subcutaneously. Schindler[33] reports favorable results in eleven cases of urticaria and fifteen cases of pruritus caused by allergic factors. Schmidt[34] reports excellent results with Antistine in the treatment of serum sickness, drug eruption, and urticaria. In his opinion, Antistine greatly relieves the pruritus in about one-half of dermatoses treated with this drug. He used oral and intramuscular therapy; the daily doses varied between 0.1 and 0.6 gram. Especially good results with Antistine are reported by Kallos.[18] All sixty-two cases of acute urticaria were improved. He used rather large doses, 100 mg. six times daily orally and/or parenterally. In Britton's[5] experience, Antistine was of benefit in only five of eleven cases of urticaria.

Benadryl.—Benadryl gave relief in about 90 per cent of acute urticaria in the experience of Lynch[22] and of O'Leary and Farber.[25] Twenty-four out of twenty-nine patients with urticaria had pronounced relief in Blumenthal and Rosenberg's[4] experience. Lynch found Benadryl especially effective in the treatment of urticarial hypersensitivity to drugs. Benadryl gave relief to about 60 per cent of eleven patients with insect bites. He also obtained approximately 60 per cent relief in patients with vulval pruritus. The results were encouraging, but inconclusive, in erythema multiforme, rosacea, and lupus erythematosus. There was failure in various forms of eczema and dermatitis herpetiformis. According to O'Leary and Farber, the edema present in scleroderma and acrosclerosis can be relieved temporarily with Benadryl therapy. In seven of nine patients with these conditions, movements of the fingers and hands were easier. Only two of the seven patients, however, had sustained relief. In 31 per cent of the patients in this series, toxic reactions to Benadryl were exhibited. In regard to atopic dermatitis, only eight of twenty-five patients of O'Leary and Farber were relieved of pruritus. However, in certain forms of contact dermatitis, Benadryl seems superior to other antihistaminics. Loveless[21] states that the itching, but usually not the lesion of poison ivy and similar eruptions of the contact type of eczematous dermatitis, yielded to Benadryl in three-fourths of the eighteen patients treated.

Decapryn.—Decapryn is another new histamine antagonist. In the experience of Brown, Weiss, and Maher,[6] generalized pruritus was relieved in one-half the patients. There was significant relief in erythema multiforme, but no relief in two patients with contact dermatitis from poison ivy. Drowsiness was the most commonly encountered side effect, and was observed in about one patient out of six. Of the patients who had previously taken other antihistaminics, most preferred Decapryn. The authors consider Decapryn a valuable addition to the antihistaminics or antiallergic agents.

Histadyl.—Histadyl showed its greatest effect in acute urticaria, according to Pierce and Mothersill.[28] In the reviewers' experience this drug has been satisfactory in pruritus ani et vulvae and in relieving the pruritus of atopic dermatitis and of the atopic eczema of the hands. In doses of 200 mg. daily, or less, the incidence of side effects has been exceedingly low.

Neoantergan.—Neoantergan malleate, in daily total doses from 0.3 to 0.8 gm.,

relieved the symptoms in eight cases of chronic urticaria in Hunter's[17] experience. Six cases of acute urticaria were treated successfully.

Pyribenzamine.—Kesten[19] treated 280 patients with dermatoses associated with marked pruritus. The average oral dose was 50 mg. after each meal and 100 mg. at bedtime. Pyribenzamine was beneficial in the treatment of approximately 68 per cent. Prompt and complete relief was obtained in patients with serum sickness and in many patients with urticaria due to penicillin. The continued use of Pyribenzamine effectively controlled most physical allergies and dermographism. Pyribenzamine completely relieved or controlled the symptoms in 65 per cent of patients with urticaria, and depressed itching in approximately 60 per cent of patients with allergic eczema, 40 per cent with dermatitis venenata, and 75 per cent with pruritus. Pyribenzamine was discontinued in about 13 per cent of the patients because of side effects. The results of Baer, Sulzberger and Witten[3] are less optimistic in regard to itching dermatoses other than urticaria. They noted a strong antipruritic effect in only about 10 per cent of these cases treated with Pyribenzamine and Benadryl.

Thephorin.—Reynolds and Horton[32] report on Thephorin. One out of three cases with acute urticaria gave an excellent result. Three cases of chronic urticaria were not relieved. However, the antihistaminic effect seemed apparent from its efficiency in cold urticaria and one case of hives following intravenous histamine therapy.

Thenylene.—Seventy-two patients with a variety of dermatologic conditions were treated with Thenylene by Kierland.[20] Best results were obtained in urticaria and angioneurotic edema. Of nineteen patients with atopic dermatitis, those who had urticarial lesions gave the most satisfactory response. Four out of five patients with anal and vulval pruritus were helped. Similar results with thenylene are reported by Feinberg.[14]

Vitamin D_2.—There appears some chemical relationship among most of the antihistaminics used so far. Apparently other chemicals also have some antihistaminic or antiallergic property. Dainow[7] treated guinea pigs with subcutaneous injections of massive doses of vitamin D_2. He injected 900,000 units of the Vi-De superconcentrate (Wander) twice at one week's interval. He was able to protect them from the bronchial spasm, which is produced by spraying histamine and acethylcholine in animals that were not treated with vitamin D. Dainow considered this as an indication that vitamin D_2 possesses antiallergic property. This explains the same author's previous observation (1939) that occupational eczemas can be favorably influenced by vitamin D_2 treatment, even if the patient continues working in the same environment.

Comparative Clinical Studies on the Action of Different Antihistaminics

Clinical comparisons of this kind are subject to various sources of error. A. and S. Friedlaender[15] have tried to overcome these difficulties in a careful comparative evaluation of Antistine and Pyribenzamine. Both drugs were at times prepared in capsule form and alternated without the knowledge of the patient. Placebo capsules were also used in eliminating as far as possible the psychologic factors involved in drug administration. Pyribenzamine was usually more beneficial in urticaria. In only one case of this type was Antistine found more helpful. Pyribenzamine appeared to be slightly more effective in relieving the distress accompanying pruritic skin conditions. In a group of seventy-two patients who received both drugs, the incidence of side effects from Antistine was 18.05 per cent, as compared to 38.8 per cent from Pyribenzamine. Of the twenty-eight patients who experienced unpleasant reactions from Pyribenzamine, eighteen were able to take an effective dose of Antistine (50 to 100 mg.) without difficulty. The remaining ten individuals experienced essentially the same reaction from either drug. On the other hand, only three out of thirteen patients noting side effects from Antistine were able to tolerate a 50 mg. dose of Pyribenzamine. Comparing the results of the same two drugs in rather small groups of patients, Watson[39] had better results in urticaria with Antistine than with Pyribenzamine, whereas in atopic dermatitis Pyribenzamine afforded greater relief. The latter observation agrees with the experience of the reviewers.

Kierland[20] noted a high degree of similarity in a clinical dermatologic comparison of Thenylene, Benadryl and Pyribenzamine. In atopic dermatitis, Benadryl made a better showing, which Kierland attributes to its greater sedative effect.

Compiling 3,600 observations from the literature and adding 200 of her own, Loveless[21] states that there is little difference between the efficacy of Benadryl and Pyribenzamine.

Antihistaminics in Contact Dermatitis

Blumenthal and Rosenberg[4] obtained encouraging results in a small series of patients with contact dermatitis. Kierland[20] obtained good results with Thenylene in individuals who had acute dermatitis venenata. The reviewer can confirm this experience. However, the efficacy of antihistamines in contact dermatitis is denied among others by Sulzberger,[35] Osborne,[26] as well as O'Leary and Farber,[25] Tweedall and O'Connor.[38] Pyribenzamine did not alter the patch test response in five patients that gave 4+ reactions to poison ivy. Only one had some relief of subjective symptoms. Mayer[23] states that experimental sensitizations of the contact type dermatitis are much more resistant to treatment with Pyribenzamine, although in almost all cases the antihistaminic compound had a definite beneficial influence. However, in no animal was there complete protection. Mayer[24] also reports that Pyribenzamine suppresses or attenuates the initial state of skin irritations in guinea pigs, produced by primary irritants. Aaron, Peck and Abramson[1] were also able to suppress or reduce the intensity of patch test reactions by preceding iontophoresis with Pyribenzamine. With the same technique, these authors also inhibited dermatologic reactions due to primary irritants in guinea pigs.

It seems to the reviewers that there are several plausible explanations for these controversial findings and opinions. The different cases of contact dermatitis are not all identical from an immunologic point of view. Epidermal sensitivity is present in most cases, but not in all.[9] However, in addition to this epidermal sensitivity there may be also dermal sensitivity, either or both of the urticarial type[38] or of the tuberculin type.[9] The former combination is found frequently in clinical poison ivy dermatitis. These cases seem to be those that respond to Benadryl in regard to subjective symptoms. Tuberculin-type sensitivity in contact dermatitis is recognized especially in those cases that are sensitive to nickel, chromates, weeds, drugs and probably also in dermatitis from paraphenylendiamine, which Mayer used in his experiments. The efficacy of antihistaminic drugs in these cases is not as pronounced or regular as in the former, but in some instances rather gratifying. Dosage may be an additional factor. In Mayer's[23] experiments 0.5 mg. to 1 mg. of Pyribenzamine per kilogram body weight gave effective protection to more than 50 per cent of sensitized guinea pigs in regard to anaphylaxis; in vascular sensitization of guinea pigs to hog serum doses of 10 to 25 mg. per kilogram body weight were required to prevent or suppress completely the symptoms. In epidermal sensitivity the same large doses were required, but still only with partial success. Inadequate dosage is also claimed for failure of clinical response to Benadryl, by Reinstein and McGavack.[31] Another factor, explaining the discrepancy of opinion of the value of antiallergic drugs in contact dermatitis may be the differences of pharmacologic action. The relief obtained may not be due to their antihistaminic efficacy, but to their anesthetic or sedative action. That could explain the superiority of Benadryl in these cases, as this drug appears to have the most pronounced sedative effect.

Topical Use of Antihistaminics

Feinberg and Bernstein[13] treated patients with itching dermatoses with a 2 per cent Pyribenzamine ointment. They obtained relief in the majority of cases, particularly atopic dermatitis and pruritus ani; Sulzberger, Baer and Levin[36] could not fully confirm these findings. They had good results in lichen simplex chronicus circumscriptus (circumscribed neurodermatitis, localized atopic dermatitis). Of sixteen cases, eight showed definite improvement and four additional cases transitory improvement in pruritus and clinical course. However, of forty patients with atopic dermatitis (disseminated neurodermatitis) only two showed transitory improvement in pruritus, twenty-five showed no change and thirteen were made worse. Of a total of ninety cases, two developed an allergy of the eczematous contact type to Pyribenzamine and two presented systemic symptoms, such as vertigo, palpitation or "jittery" sensations.

Aaron, Peck and Abramson[1] treated a total of twenty patients with iontophoresis of Pyribenzamine. There were seventeen cases of chronic lichenified eruptions and one case each of Sulzberger and Garbe's syndrome (see above), generalized exfoliative dermatitis and atopic dermatitis. In every case there was some relief from pruritus and clinical improvement. There was a complete remission in the majority of cases. Ten per cent and 5 per cent solutions of Pyribenzamine were

used, which were introduced into the skin through the positive electrode. Daily (localized atopic dermatitis). However, this cream has been quite helpful in a few case where oral Pyribenzamine had failed.

Perry[27] used a 2 per cent cream of Benadryl in a water-soluble base. Local application of this cream did not influence the erythema and wheal produced by an intradermal injection of histamine. Of twenty patients with various pruritic dermatoses, six had moderate and two had excellent relief from the ointment base alone.

Experience with a 2 per cent Histadyl cream[10] has also shown that the best indication for antihistaminic creams is the circumscribed lichen simplex chronicus (localized atopic dermatitis). However, this cream has been quite helpful in a few cases of generalized atopic dermatitis, as well as infantile eczema of the atopic type and in pruritus ani et vulvae, although it has failed in quite a number of similar cases. The differences of opinion and results regarding antihistaminic ointments may be attributed not only to the different antihistaminics and ointment bases, but also to the selection of cases. Water-soluble creams should be used only in chronic eczemas, not during the acute phase.

The side reactions of the antihistaminics are reviewed in the chapter on drug eruptions.

General reviews about the antihistaminics are presented by Feinberg,[12] Hartman,[16] Rajka.[29]

Other Antipruritic Drugs

A number of vasodilator drugs are effective antipruritic agents. In an attempt to find a vasodilator free of undesirable side effects, Wirth[40] tried papaverine hydrochloride, an opium derivative. It is a mild sedative and may cause sleepiness when given in large doses. Papaverine hydrochloride was taken by a group of twenty-nine patients uncomfortable because of itching due to various causes, including dermatitis venenata, postscabetic sulfur dermatitis, insect bites, et cetera. The drug exerted an antipruritic effect in all twenty-nine cases—complete in twenty-six and moderate in three. Intravenous injection (1 grain), given slowly, gave consistent prompt relief lasting one to six hours. Oral administration (grains 1½) gave relief in about thirty minutes, but papaverine hydrochloride may be ineffective by mouth.

Ervin Epstein[8] treated seventeen patients suffering from various itching dermatoses with intramuscular injections of aminophylline. In all instances the itching had resisted conventional antipruritic measures. The dosage was 0.5 gm. of aminophylline administered intragluteally in 2 c.c. of fluid. In seven patients the relief of itching was dramatic; the itching subsided within thirty to forty-five minutes and did not recur until twelve to thirty-six hours later. However, the over-all results were not so successful as some of the other patients experienced temporary relief only. A high frequency of reactions was noted. These included numbness and stiffness of leg, pain at site of injection, nausea and symptoms of shock. It seems, therefore, that the toxicity and the short duration of its effect would prevent the general use of intramuscular injections of aminophyllin as an antipruritic agent.

Hydrillin (Benadryl and aminophylline) seemed to relieve the pruritus in several cases of disseminated atopic dermatitis as well as the generalized id-like eruptions associated with some cases of contact dermatitis,[11] especially in older patients. One tablet of 100 mg. Hydrillin was given four times a day.

In general, however, the older systemic antipruritics are taking a back seat behind the antihistaminics. Ergotamine tartrate relieves pruritus,[2] but gangrene may result. Lichtman in 1931 gave 1 mg. three times a day and stopped as soon as there was relief. He got good results. But later workers had some unfortunate experiences, including death after four days in one case, and amputation of both legs for gangrene in another. Though these ill effects are rare, the risks are too serious to warrant the use of the drug, when the antihistamine drugs are available instead.

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Drug Eruptions

Several recent articles have discussed the general concepts of drug allergy.[28,64,113] Dragstedt[28] divides drug idiosyncrasies into the allergic and nonallergic and offers the following provisional criteria to distinguish between the two types: (1) An allergic basis seems to be indicated when the pattern of the toxic reaction is consistent with that of the allergic disorders produced by antigenic agents. This means that reactions characterized by urticaria, dermatitis, angioneurotic edema, and asthma are probably allergic in character; that reactions characterized by jaundice, acute yellow atrophy of the liver and optic atrophy are probably not allergic, while granulocytopenia, anemia, thrombocytopenia, and polyneuritis may well be one or the other. (2) An allergic basis seems to be indicated when a priming or sensitizing administration of the drug appears to be a factor in the history, while a nonallergic basis seems to be indicated when either long continued administration or the use of substantial doses appears of major importance. (3) An allergic basis seems to be indicated when the untoward reactions are alleviated by epinephrine, diphenhydramine hydrochloride (Benadryl Hydrochloride N.N.R.) and similar agents, whose ameliorating effects are most reasonably interpreted on the basis of an antiallergic effect. A nonallergic basis seems to be indicated for those reactions which are alleviated by ascorbic acid, folic acid, thiamine and other agents whose ameliorating effect is not reasonably credited to an antiallergic effect.

PROGRESS IN ALLERGY

PENICILLIN

Parenteral Penicillin Administration.—The various reactions to parenteral injections of penicillin have been reviewed by several authors.[45,52,,74,78,79,98,104] According to Peck,[78] there are two distinct reactions of sensitivity to penicillin. One is the serum sickness-like urticarial type which is an induced sensitivity, and the other is the eczematoid-trichophytid-like type which may be based on a previous sensitivity produced by a fungus infection. To this latter group belong the so-called "spontaneous" penicillin sensitive cases. Steingold[98] believes penicillin reactions are more common in males than in females.

Exfoliative dermatitis occurring during penicillin administration appears to be of rare occurrence. In the discussion which followed Templeton's paper on cutaneous reactions to penicillin,[104] Lehman reported that he had seen two cases of exfoliative dermatitis originating from this source, and Wile reported seeing six such cases. In all instances the condition was mild and not comparable to exfoliative dermatitis due to arsenicals. Farrington and Tamura[36] reported the case of a seventy-eight-year-old man, ill with pneumonia, whose critical condition necessitated continuing penicillin therapy in spite of a maculo-papular reaction. An exfoliative dermatitis ultimately developed. Later, when the skin was clear, the patient showed urticarial and tuberculin-type reactions on testing with various commercial brands of penicillin. Patch tests were also positive. There were no reactions from autoclaved material or penicillinase-inactivated extracts.

One of the most unusual reactions to penicillin is that reported by Call and Gilbert.[15] Their patient received penicillin injections eight times within a one-year period. After each episode, abscesses developed at the penicillin injection sites. Since the injections had been given at several different army hospitals, it seemed incredible that the penicillin was contaminated in each instance. In studying this patient, the authors were able to produce a sterile abscess at the site of a penicillin injection while controls, injected with the same solution, remained normal. There is no similar case reported.

Kendig and Toone[56] reported three cases of delayed "serum sickness" type penicillin reaction occurring in the same family within a six-week period. All three patients manifested moderate fever, malaise, arthralgia, and urticaria. Two of the cases had previously received penicillin.

Barefoot and Orlandky[6] have reported an interesting case. Their patient was given injections of noncrystalline sodium penicillin on two occasions at an interval of ten days. On each occasion only a few injections were given because the patient developed urticaria. In addition to this, on the second occasion there was also a flare-up of a chronic tinea cruris and a chronic dermatophytosis of the feet. At this time intradermal tests showed a definite reaction to noncrystalline sodium penicillin while crystalline penicillin produced no reaction. Thereupon, the patient was given and tolerated full therapeutic doses of crystalline penicillin G. The authors pointed out that, in some patients at least, reactions have been observed with the use of commercial penicillin which are due to the incorporated impurities rather than the penicillin *per se*. Steingold,[98] in reviewing four cases of penicillin urticaria, performed intradermal tests with pure and commercial penicillin. All four patients showed reactions to commercial penicillin but not to pure penicillin. This author also believed the urticaria was an allergic response to impurities in the commercial preparation. Peck and Siegal,[78] after sensitizing a guinea pig with amorphous penicillin, were able to demonstrate a positive Dale reaction with amorphous but not with crystalline penicillin. This adds further proof to the impression that impurities in commercial penicillin probably are responsible for some of the allergic reactions seen.

Local Use of Penicillin.—Papers concerning the topical use of penicillin in dermatology have been presented from several sources. MacKenna[65] reviewed the principal British contributions on this subject. Hellier[50] indicated that the number of skin conditions which respond dramatically to local penicillin is actually quite small. Hopkins and Lawrence[53] sought to answer the question: Does treatment of superficial lesions with penicillin sensitize some individuals sufficiently to prevent internal treatment which might later be critically needed for some general infection? These investigators found that only about one half of the patients whose sensitivity was demonstrable by patch or intradermal tests reacted when tested by intramuscular injection. Moreover, it was shown that epidermal sensitization to penicillin is frequently local and transitory, and reactions are comparatively mild. It was concluded that sensitization to penicillin by topical application severe enough to prevent or prohibit systemic treatment with penicillin occurred in less than 1

per cent of such cases. Meara[68] described three cases of dermatitis which had skin sensitivity to certain penicillin preparations. In all three it was found that the penicillin was not the responsible agent.

Other Routes of Penicillin Administration.—There appears to be a considerable difference in the sensitizing potential of penicillin when applied to different areas of the skin and to different mucous membranes. The apparent greater susceptibility of the face and mouth to sensitivity reactions from contact with penicillin as compared to other body regions and mucosal structures has been noted by Farrington.[34,35] Hopkins and Lawrence,[53] in studying sensitization from topically applied penicillin, demonstrated that often only restricted areas of the skin showed epidermal sensitivity.

In using penicillin aerosol for respiratory infections, stomatitis, nasal irritation, and dermatitis around the nose and mouth occurs in about 5 per cent of patients.[38,82] Stomatitis after oral administration of penicillin has been observed in 14 per cent of patients so treated.[35] This is in marked contrast to the utter lack of sensitivity reactions following vaginal administration of penicillin. This route of administration was apparently first utilized by Goldberger et al.[42] They demonstrated that penicillin is readily absorbed through the vaginal mucosa and appears in the blood in high therapeutic levels. Absorption from the vagina was found to be somewhat slower and more prolonged than absorption after intramuscular injections. Wide individual varieties in blood levels obtained may, in part, be due to leakage from the introitus. The method has the advantages of being painless, and the patients may insert the suppositories themselves. In ten patients treated by this method no untoward local or systemic toxic effects were observed. Pierce, as quoted by Farrington,[35] has used vaginal suppositories containing 300,000 units of penicillin in over 500 obstetrical patients immediately after delivery without encountering a single toxic or allergic reaction. Goldman and Feldman,[44] studying the sensitizing properties of penicillin for the vaginal and rectal mucosa, observed no reactions when suppositories containing 100,000 units of penicillin were used by thirty patients over an average period of one week. These authors also devised a method of contact testing of the vaginal mucosa. No reactions were seen in five patients tested with penicillin. Abel et al,[1] while investigating the use of penicillin vaginally, found that the degree of absorption and the resulting blood levels were unreliable and unpredictable. They advocated that this route of administration be used only for inflammatory conditions localized to the vaginal area. It is interesting to note that two of nineteen nurses being used as control subjects developed urticaria during the study of vaginal penicillin absorption.

Demonstration of Circulating Antibodies in Penicillin Sensitization.—Evidence in favor of the presence of circulating antibodies in at least some penicillin reactions has been presented by Holden[52] and Templeton et al.[104] These investigators performed passive transfer tests using serum from patients with penicillin reactions. They were able to demonstrate reactions at the test injection sites when challenged with a penicillin solution. Peck and Siegal[78] were not able to demonstrate the presence of anaphylactic antibodies when the serum of a patient with known penicillin sensitivity was injected into guinea pigs prior to performing the Dale test. However, as realized by these investigators, no general conclusions can be drawn from an isolated observation.

Penicillin Desensitization.—If a reaction occurs during parenteral penicillin therapy it does not necessarily preclude the possibility that penicillin may be tolerated at a later date. There is evidence to show that penicillin sensitivity may be of relatively short duration and may decline rapidly.[53] In some instances the sensitivity to penicillin will decrease over a period of six months to a year so that a second course may be given without reaction.[84] The interval may be shorter, but certainly only rarely less than six weeks.[98] On the other hand, each subsequent attack may tend to increase the degree of sensitivity still further with increasingly severe reactions.[112] As a general rule, it is advisable to test such patients with small trial doses to determine if sensitivity still exists before again starting full therapeutic doses. Positive intradermal tests are not in themselves sufficient reason to assume that sensitivity of such a degree exists as to preclude intramuscular injections of penicillin. The intradermal test may be positive and the patient still tolerate penicillin administration via the intramuscular route.[53] If a reaction recurs with a trial dose, desensitization may be attempted.[3,79,89] Peck et al[79] have reported the case of a sixty-three-year-old man who had previously developed a generalized eruption following penicillin injections. One month later a forty-eight-hour intradermal test to noncrystalline penicillin was

positive. Four months later it became imperative to give him penicillin again. Intradermal tests were still positive. Thereupon, an attempt at desensitization was undertaken. Injections were given subcutaneously three times a week starting with 400 units of noncrystalline penicillin. Each subsequent dose was doubled. When the dose reached 20,000 units, a skin test with penicillin gave only a pinhead sized papule at forty-eight hours. Intramuscular injections were then started and built up to 30,000 units every three hours. At this time a cutaneous reaction appeared in the groins. Treatment was stopped for twenty-eight hours, the dosage reduced, started again, and gradually brought back to the maximum level. The eruption in the groins gradually faded. The patient was later tested with both crystalline and commercial penicillin with negative results.

Intravenous Procaine Treatment of Penicillin Reactions.—Intravenous procaine has been used in treating serum sickness-like penicillin reactions according to the procedure outlined by State and Wangensteen. Dressler and Dwork,[30] in treating a patient with such a reaction, observed dramatic subsidence of the urticarial rash, and regression of the leukocytosis, fever, and arthralgia. Cohen and Kaufman[20] treated four cases of serum-like reactions due to penicillin with intravenous infusions of procaine. Two of the cases showed a favorable reaction. The other two did not respond. These authors cautioned of the possible dangers involved in this procedure. This warning was given earlier by Waldbott,[108] who pointed out that sensitivity to cocaine and related drugs is not uncommon and allergic shock may occur during such infusions. Preliminary skin tests are unreliable. He reported a case where the patient developed severe allergic shock after receiving 0.5 gm. procaine hydrochloride intravenously for relief of an urticarial reaction from penicillin. On the other hand, Graubard et al[47] have administered over 2,000 intravenous procaine infusions for control of pain without serious complications. It would appear that allergic reactions from intravenous procain are uncommon. Nonetheless, they constitute an ever-present danger. The procedure should be done in a hospital under controlled conditions, and then only after careful consideration. Pillsbury and his group,[81] using Benadryl and Pyribenzamine, have outlined a more conservative approach to the management of urticaria due to penicillin. Dreisbach,[29] in animal experiments, has shown that any effect obtained in this condition with the antihistaminics is subjective and is probably due to central depression or local anesthetic action. This investigator has expressed doubt that free histamine is liberated in the skin sensitization reaction to penicillin and horse serum.

Cross Sensitization to Penicillin and Trichophytin.—There appears to be a difference of opinion regarding the presence of a common antigen in trichophytin and penicillin. Cormia, Lewis and Hopper,[21] after a series of guinea pig experiments, presented evidence of a crossed reactivity in penicillin and trichophytin sensitization. Their results confirmed the supposition made by many workers that a common antigen is present in penicillin and in pathogenic fungi causing superficial fungus disease. They believe that the shock-like reactions developed shortly after institution of penicillin therapy are due to pre-existing sensitization by pathogenic fungi. On the other hand, Peck and Siegal[78] were not able to demonstrate a single positive Dale reaction to trichophytin in guinea pigs injected with amorphous penicillin. This, plus other observations, led these authors to conclude that the dermatophytes produce penicillin or a penicillin-like substance and thus sensitize the skin to this substance just as they do to trichophytin. Penicillin sensitivity, thus induced, is independent of trichophytin sensitivity. They are often associated because of their common origin. These authors proved, by a series of clinical observations and experiments, that there is no common antigen between crystalline penicillin and trichophytin. Penicillin sensitivity can exist in the absence of trichophytin sensitivity.

Dangers in the Indiscriminate Use of Penicillin.—Aside from the development of sensitivity, there is another good argument against the indiscriminate use of penicillin. The widespread use of the drug, particularly in inadequate dosage, is a potent factor in breeding resistant strains of organisms.[32] Barber[5] has pointed out a notable increase in the resistance of certain organisms, especially staphylococci, to penicillin year by year since the drug was first introduced. In analyzing a series of 100 patients with staphylococcal infections seen during the first half of 1947, this investigator found no less than thirty-eight with penicillin-resistant strains! According to Florey,[39] there is no significant cross resistance between the various antibiotics, e.g., a penicillin-resistant staphylococcus may be rather sensitive to helvolic acid or many other antibacterial substances. He hastened to add, however, that most of these other antibiotics which have been investigated are toxic to animal

tissues or have other disadvantages. It would appear that penicillin is quickly expending its usefulness. However, Voureka[107] has recently dispersed some of the gloom associated with this problem. From his studies it appears that when some penicillin-resistant strains grow in association with other bacteria—a condition which may happen in the body—they lose their resistance and again become penicillin susceptible. Voureka's work along these lines is continuing, and other valuable information may be forthcoming.

Experiments have shown that penicillin in high doses exerts a pharmacologic oxytocic action on isolated strips of guinea pig uterine muscle.[78] These experimental observations lend support to the contention of some that penicillin during pregnancy may be responsible for early miscarriages.

Streptomycin

This antibiotic, derived from the actinomycetes, is the drug of choice in many infections due to Gram-negative bacilli and to Mycobacterium tuberculosis. Four general types of toxic reactions to streptomycin have been observed: (1) the so-called histamine reaction, characterized by flushing, headache, and an abrupt fall in arterial pressure, (2) various other manifestations of sensitivity, (3) a neurologic disturbance characterized by vestibular dysfunction and occasionally by deafness, (4) evidences of renal irritation manifested by cylindruria and occasionally accompanied by impairment of renal function. The histamine-like reactions reported by early investigators were probably due to impurities in the drug. However, the other types of toxic reactions have continued to appear even with the use of highly purified material. Some of these reactions may still be due to remaining impurities, but it is probable that some of the pharmacodynamic effects observed are intrinsic properties of the drug.[70] The various sensitivity reactions to streptomycin are chiefly of interest to us. Contact dermatitis, developing in those administering the drug, is discussed elsewhere in this review.

Eruptions developing during streptomycin therapy have been reported from several sources.[2,24,37,55,83,97] The type of eruption is by no means constant. For example, maculopapular, erythematous, erythema-multiforme-like, urticarial eruptions and exfoliative dermatitis have all been mentioned. Eruptions have occurred most commonly in those undergoing long courses of streptomycin therapy, such as is required in the treatment of tuberculosis. Chinn et al,[17] treating seventy-seven gonorrhea patients, observed no skin reactions following single injections of streptomycin in doses varying from 0.1 gm. to 0.5 gm. Where treatment has been prolonged, eruptions have occurred most often between the seventh and tenth days.[24,37,83,97] To Steiner and Fishburn[97] this occurrence recalled Milian's "erythema of the ninth day" which supposedly is due to an activation of a pre-existant latent injection (biotropism). These authors felt that eruptions from streptomycin were not of a toxic but of an allergic nature. And such they no doubt are. The incidence of eruptions occurring during extensive streptomycin therapy has been reported as 18 per cent,[97] 12 per cent,[37] 7.5 per cent,[55] and "a considerable percentage of cases."[24]

In cases where the eruptions are mild and without systemic reaction, treatment with streptomycin may apparently be continued without any untoward sequelae. Thus, Steiner and Fishburn,[97] and Kane and Foley[55] did not consider the mild eruptions which they observed as contraindications against further necessary or desirable treatment with streptomycin. There were no ill effects. On the other hand, when a generalized exfoliative dermatitis threatens or develops, it constitutes an indication for immediate cessation of therapy. Seven such cases (0.80 per cent) were recorded in the Report of the Council on Pharmacy and Chemistry.[24] Unfortunately, the details of these cases were not given. In the Report of the American Trudeau Society[2] mere mention is made that exfoliative dermatitis is observed very rarely. Pulaski and Seeley[83] observed four instances of exfoliative dermatitis among 1,153 patients treated with streptomycin. Where there is any question of the dangers involved, it is probably advisable to discontinue treatment and resume it later when evidence of hypersensitivity has disappeared. This was the procedure followed by Farrington and his group[37] in two cases who developed a pruritic skin eruption with a rise in temperature, nausea and vomiting, and hypotension after nine days of treatment. In both, clinical evidence of sensitivity subsided in one week. Thereafter the patients were tested every week with small doses of streptomycin, and mild symptoms were reproduced while sensitivity still existed. At the end of four and eleven weeks, respectively, evidence of sensitivity could no longer be demonstrated and a full treatment schedule was resumed.

The Report of the Council on Pharmacy and Chemistry[24] states that Benadryl was usually effective in relieving the pruritus of streptomycin eruptions. However,

Steiner and Fishburn found that the eruptions were apparently little influenced by treatment which in their cases consisted in the main of calcium gluconate, Benadryl and ephedrine.[97]

Some degree of eosinophilia (commonly of the order of 10 to 20 per cent) is observed early in the course of treatment with streptomycin whether or not a skin eruption is produced.[24,37,97] It is frequently intermittent and often persists until treatment is stopped. It is not of itself an indication for cessation of treatment.[24]

Peck and Siegal[78] showed that in guinea pigs injected with penicillin there was not a single Dale reaction to streptomycin. In the streptomycin-injected animals, however, two of the animals showed reactions to amorphous and crystalline penicillin. These experiments suggest that streptomycin as now available contains an antigen closely related to penicillin. It may even be penicillin itself. The authors therefore suggest caution in employing penicillin in patients who have shown reactions to streptomycin.

Tyrothricin

In contrast to penicillin and streptomycin, tyrothricin, an antibiotic derived from bacteria, appears to have a very low sensitizing index. In fact, these reviewers have been unable to find a single report of serious untoward reaction from topically applied tyrothricin. Sulzberger and Baer[100] have reported using Tyrothricin Intraderm in hundreds of cases without encountering an instance of true eczematous sensitization. The drug is limited in its applicability in that it can only be used topically. Goldman et al[43] reported using tyrothricin in 1:5000 concentration on resistant skin infections in eleven patients. There were no signs of irritation. The use of the drug in rhinology and surgery was likewise encouraging. However, Otenasek and Fairman[77] reported two cases in which chemical meningitis developed after the frontal sinuses had been irrigated with a tyrothricin solution. Darling and Baumeister[25] treated 250 patients with nose drops containing tyrothricin suspended in a synthetic vasoconstrictor solution. Untoward effects were not mentioned.

Sulfonamides

The sulfonamide drugs were all but forgotten in the wave of enthusiasm which accompanied the introduction of the antibiotics. Fortunately, investigation and study of these compounds has continued. In the face of ever-increasing organism resistance to the antibiotics, especially penicillin, these drugs are again assuming an important place in the physician's armamentarium. In fact, there is now an impression abroad (not statistically proven) that one of the sulfonamides (sulfamerazine) is more effective than penicillin in the treatment of pneumonia.[54] In accepting the partial comeback of the sulfonamides, we must not overlook the costly lesson of the past nor accept isolated reports of low toxicity without reserve. Carver and Yonkman[16] reported on the use of 2.5 per cent sulfathiazole in propylene glycol as a mucus membrane spray in upper respiratory infections. Of "several score" patients treated there was no evidence of sensitization. Ballenger[4] found only seven instances of sensitization among 1,500 patients who received an average of 2.5 insufflations of powdered sulfonamide compounds for acute infections of the nose and throat. Clark[18] was favorably impressed with the local use of a 1 per cent solution of Sulfamylon (para-[amino-ethyl]-benzene sulfonamide hydrochloride) in surgical eye cases. In eighty-four cases treated there were no toxic reactions. Fox[40] used Sulfamylon as a spray in more than 200 cases of rhinosinusitis in 137 patients. No case of drug sensitivity was encountered, even though a number of patients used the drug on several occasions when they suffered repeated attacks of acute sinusitis.

Burger[14] recorded an interesting case of a soldier who developed edema of the face and hands, pruritus, erythema, and vesicle formation about the lips and chin on two occasions after oral ingestion of sulfathiazole. Later, when a sulfathiazole ointment was used as a venereal prophylactic, all the previously affected areas erupted but not the genitals. This case demonstrates that after sensitization to a sulfonamide occurs once, later exposure to the same drug can produce identical reactions whether the drug is taken orally or applied locally.

A new sulfonamide, 3, 4 dimethyl-5-sulfanilamido-isoxazole, has proved to be effective against E. coli and Proteus vulgaris. Narins[73] observed toxic symptoms in four of fifty patients treated with full therapeutic doses. Two patients developed dermatitis and two experienced nausea.

Studies on sensitivity to topically applied sulfonamides have proved enlightening. Sulzberger et al[102] made a study of 254 volunteers who were divided into four groups. Each group was treated with a cream containing one of four sulfonamides. These creams were repeatedly applied in the treatment of experimental standard

thermal burns on both arms. The results were as follows: Of forty-nine men treated with 5 per cent sodium sulfadiazine cream, 57 per cent developed a dermatitis. Of fifty-four men treated with 5 per cent sulfanilamide cream, 22 per cent developed a dermatitis. Of seventy-two men treated with 5 per cent sulfathiazole cream, 7 per cent developed a dermatitis. Of seventy-nine men treated with 5 per cent sulfadiazine cream, 5 per cent developed a dermatitis. In 48 per cent of the cases which developed dermatitis, the eruption appeared within two to eight days after the commencement of the local application. Only in the sodium sulfadiazine series did there seem to be a significant direct relationship between the number of applications and the incidence of dermatitis. Perhaps the size of the exposed area was also a factor here. Once a man developed a clinical sensitization dermatitis, he could not be treated again with the same sulfonamide without again developing a dermatitis. Only 31 per cent of the men who developed dermatitis subsequently showed a positive patch test with the offending sulfonamide. However, the patch test was positive in all cases who had a severe dermatitis. Of twelve men who developed dermatitis after topical application of sulfonamide cream, eight developed dermatitis and one, general symptoms and itching, upon the subsequent oral administration of 6.0 gm. of sulfadiazine. Of thirty-one men who received repeated applications of sulfonamide cream but who did not develop a dermatitis, five suffered from general symptoms but no dermatitis when later given 6.0 gm. of sulfadiazine orally. Of thirteen controlled subjects who had had no known previous exposure to sulfonamide, none developed dermatitis or general symptoms from the same oral dose of sulfadiazine. Apparently the sensitizing potential of various sulfonamides, when applied topically, corresponds directly to their solubility in water. Sodium sulfadiazine was a frequent offender, sulfanilamide was next, then sulfathiazole, and lastly sulfadiazine. The incidence of sensitization by externally applied sulfonamide is directly proportional to the preceding superficial skin damage at the site of application. Previous exposures to, and/or skin sensitization by, externally applied sulfonamide materially increases the risk of cutaneous and general reaction on subsequent oral administration of the same or related drugs.

Gottschalk and Weiss[46] patch-tested over 200 subjects, using three different sulfonamide ointments. Ten days to two weeks later the same patients were again patch-tested with the same materials. It was found that the number of persons sensitized by the patch tests was small: 2.3 per cent were sensitized by a 5 per cent sulfadiazine ointment (base pH 7 to 7.5), 0.49 per cent were sensitized by a 5 per cent sulfathiazole ointment (base pH 7 to 7.5), and 0.0 per cent were sensitized by a 5 per cent sulfadiazine ointment (base pH 8.1). These investigators concluded that the sulfonamide drugs are not highly potent cutaneous sensitizers *if* applied to only a small area of the skin and *if* applied for a period of less than five days. They agreed with Sulzberger's group that the danger of sensitization is greatly increased when the drugs are applied to previously damaged skin.

Many attempts have been made to clarify the allergic mechanisms involved in sulfonamide sensitivity. Results have been inconstant. In patients with known sulfonamide sensitivity some have been able to demonstrate that sensitivity by one or more methods (patch, scratch, intradermal, or passive transfer) while others have failed. As pointed out above, Sulzberger and his group[102] were able to demonstrate sensitivity by patch test in only 31 per cent of subjects who were known to have a sulfonamide sensitivity. Several investigators[96,111] have recently proved by successful passive transfer tests the existence of circulating antibodies in two cases of sulfadiazine sensitization.

To the many eruptions already attributable to the sulfonamides Philpott[80] has added another. He has reported three cases in which a psoriasiform dermatitis appeared following the oral administration of one of the sulfonamide group. A clinical diagnosis of psoriasis was made in each case. This phenomenon has been discussed elsewhere,[105] and while generally acknowledged to occur, the pathogenesis remains obscure. Do the sulfonamides cause the eruption or is it simply an aftermath of the condition (sore throat, et cetera) for which the sulfonamide was originally prescribed?

The Antihistaminics

These drugs are considered here solely from the standpoint of their side effects and toxicity. The side effects of Benadryl and Pyribenzamine are well known and are listed merely for the sake of completeness. Those of Benadryl include drowsiness, dizziness, weakness, dryness of mouth, nausea, nervousness, confusion, poor co-ordination and gastrointestional complaints.[76] Those of Pyribenzamine include chiefly sedation and gastrointestinal disturbances such as nausea, bad taste in the mouth, anorexia, heartburn, epigastric distress, abdominal cramps, and

occasionally vomiting and diarrhea.[62] Loveless,[63] in a comparative study, noted sedation in 61 per cent of her patients taking Benadryl while only 20 per cent of patients on Pyribenzamine manifested this symptom. O'Leary and Farber[76] observed side reactions in 31 per cent of patients taking Benadryl. As a rule, these side effects are not of a serious nature, and with continued administration a "tolerance" may be established.[67] However, a number of unusual reactions have been reported in the literature of the past year. Steinberg[99] reported hysteria of a severe degree occurring in a patient taking 350 mg. of Benadryl daily for control of hay fever symptoms. When the drug was discontinued, normalcy was regained within forty-eight hours. Weil[110] reported an epileptiform seizure in a three-and-a-half-year-old boy following ingestion of 100 mg. of Benadryl. Of course, this dose was considerably in excess of the recommended daily dose of 2 mg. per pound of body weight. Geiger et al[41] reported a shock-like reaction occurring in a twenty-five-year-old woman. This patient took 50 mg. of Benadryl t.i.d. After a total dose of 300 mg. had been reached she experienced palpitation, dimmed vision, malaise, and nausea. Following another 50 mg. dose she was found in bed, cold, pale and pulseless. Complete recovery was attained in three hours following administration of epinephrine. Later Benadryl again produced the same symptoms. A prolonged reaction to Benadryl was observed by Schwartzberg and Willerson.[95] An adult man took twenty-three 50 mg. capsules of Benadryl over a twenty-day period. Ingestion of the drug was irregular, but the patient never took more than three capsules on any one day. Progressive symptoms (intensifications of ordinary side reactions) appeared after one week. When the medication was stopped, recovery was slow. At the end of a three-month period practically all toxic symptoms had subsided. Barksdale and Hall[8] observed the development of a skin eruption in two patients on Benadryl. They suggested that the Benadryl may have been responsible, but further proof was lacking. The same authors observed three patients who possibly exhibited withdrawal symptoms when they became nauseated on stopping the drug.

Brown and Crepea[12] described a case in which asthma developed following ingestion of Pyribenzamine tablets. Investigation revealed that the patient was sensitive to the gum tragacanth used in compounding the tablets. This case very nicely demonstrates that other constituents should be investigated before ascribing sensitivity reactions to the main ingredient of a medication. Two reports have appeared of eruptions occurring in the wake of Pyribenzamine administration. Epstein[33] has described two cases. The first case suffered from a chronic atopic eczema. An erythematous macular eruption, following the lines of body cleavage, appeared on the arms, legs, and trunk within twelve hours after oral ingestion of Pyribenzamine. This dermatosis resembled pityriasis rosea. After the drug was discontinued, the lesions disappeared and reappeared when Pyribenzamine therapy was resumed. The second case also had a chronic eczema. Pyribenzamine was administered, and less than ten hours later, papular erythematous lesions appeared and spread rapidly over the whole body. Two weeks later the eruption disappeared, and the original eczematous lesions remained. Additional history revealed that another physician had prescribed the same medication two months before. The ingestion of one tablet had caused an immediate generalized eruption of the same type. Harris and Shure[49] reported a case of a woman who developed a vesicular eczematoid eruption while taking Pyribenzamine. There was no previous history of dermatitis. After subsidence of the eruption Pyribenzamine tablets were given a second and third time in disguised form. Each time the eruption was reproduced. This patient had taken many medications in the past, including aspirin, various headache tablets, laxatives and vitamin pills without untoward reactions. Therefore, the authors felt that her sensitivity was due to Pyribenzamine and not to another ingredient used in compounding the pills. Unfortunately in none of the three reported cases of dermatitis was a trial made with chemically pure Pyribezamine.

Granulocytopenia probably due to Pyribenzamine has been reported by Blanton and Owens.[11]

Apparently there are no contraindications to the use of the antihistaminics during pregnancy.[86]

BAL (2,3-DIMERCAPTOPROPANOL, BRITISH ANTI-LEWISITE

Very favorable reports on the use of BAL in heavy metal poisoning continue to appear in the literature.[10,19,26,57,61,66,90,91,94] Reeve[91] has called this useful drug "the answer to the syphilologist's prayer" because it has relieved the dread of arsenical reactions. The internist might also rejoice over the effectiveness of BAL in combating the toxic effects of gold arising during treatment of rheumatoid arthritis. The need for such an agent becomes apparent in the light of a recent report by

Browning et al[13] on gold therapy in forty-seven patients with rheumatoid arthritis. A high incidence of toxic reactions to gold was noted, 62 per cent of the patients being involved. Although most of these reactions were of little consequence, there were two cases of exfoliative dermatitis, with one death. Stomatitis,[19,66] anal ulceration,[66] exfoliative dermatitis,[19,26,66] pruritus,[19,26,90] thrombocytopenic purpura,[61] granulocytopenia,[61] and conjunctivitis,[19,66] each a toxic sequela of chrysotherapy, have responded to BAL. To be effective in combating reactions the drug must be used early, at least within two months from the onset of toxic symptoms,[87,88,90] although treatment of exfoliative dermatitis even after this length of time may afford some amelioration of symptoms.[66] There are indications that BAL may be of value in the management of lead poisoning.[103] It is useless in the treatment of argyria.[85]

Unfortunately, BAL has a toxicity of its own. Among its side effects are malaise, nausea, vomiting, burning of the skin, burning sensation of the gums, nose, and eyes, excessive salivation, lacrimation, parethesia, perspiration, sense of warmth, pain in the legs, arms, abdomen, and head.[106] Cohen et al[19] reported such symptoms of BAL intoxication in three of six patients treated. These symptoms are, as a rule, transient and may be disregarded in view of the benefit obtained. Tye and Siegel[106] gave ephedrine sulfate to a patient in whom BAL caused symptoms similar to a serum sensitivity reaction and succeeded in alleviating the discomfort. A second patient with toxic symptoms from BAL likewise responded. These authors pointed out that the preparation of the patient with ephedrine sulfate (25 mg.) shortly before the injection of BAL may lessen the intensity or prevent entirely the side effects of this valuable remedy. Green and Russell[48] claim that the symptoms of toxicity to BAL can be explained on the basis of tetany due to depletion or unavailability of calcium or magnesium or both.

Sulzberger, Baer, and Kanof[101] reported their experiments with BAL containing preparations applied to the skin of rabbits and human beings in a study of comparative effectiveness in decontamination, treatment and protection against damage by lewisite and other arsenical vesicants. They found that when a 5 per cent concentration of BAL was employed, the vehicle in which the drug was incorporated did not appear to exert a great influence on the decontamination and therapeutic efficacy of BAL. However, the protective efficacy of the BAL was greatly influenced by the vehicle in which it was contained. On the basis of their findings and recommendations, relatively stable and effective BAL preparations were made available to our armed forces during the recent war.

Cornbleet[22] recorded his observations and findings of his personal sensitization to BAL. The dermatitis appeared on the regions of the hands used in grasping a syringe. A 1 per cent concentration of BAL in peanut oil gave a positive patch reaction. His attempts to demonstrate cross sensitivity to related compounds are discussed elsewhere in this review.

5-Nitro-2-Furaldehyde Semicarbazone (Furacin)

This is one of a series of chemicals known as the "furans" which are derived from oat bran. It is both bacteriostatic and bacteriocidal and has been shown to be effective in the local control of both Gram-positive and Gram-negative organisms. The original report on the use of this substance in dermatology by Downing, Hanson, and Lamb[27] was enthusiastic, but the high incidence of sensitization to the drug (3 per cent) could not be entirely overlooked. The Council on Pharmacy and Chemistry[23] advised caution in using the drug for a period longer than five days because of the danger of sensitization. There is a possibility that the water-soluble base in which the substance is incorporated may be responsible in part for the sensitization reactions so far reported. Further investigation along these lines is indicated. At any rate, before Furacin dressings can come into general use, the hazard of sensitization must somehow be reduced.[31] Morin[71] reported a moderate case of sensitization to Furacin after six weeks' use of the medication. An erythematovesicular eruption appeared at a graft site which was being treated with Furacin and also at a donor site which was healed but which had previously been treated with the drug. Hill and Flood[51] have reported a psoriasiform eruption appearing twenty-four hours after the use of a Furacin ointment. Although patch tests were negative, these authors held the drug responsible. The eruption subsided uneventfully in ten days.

Bistrimate (Sodium Bismuth Triglycollamate)

It was generally thought that the search for a satisfactory oral bismuth preparation was completed when Sobisminol was introduced in 1939. However, it was soon realized that gastrointestinal disturbances were frequent with the use of this

drug, and it fell into disuse. The next and latest oral bismuth compound to be introduced is Bistrimate (Sodium Bismuth Triglycollamate). This compound contains 18.3 per cent bismuth and is readily soluble in water. Lehman and Fassett[59] have reported extensively on the experimental use of the drug in mice, rabbits, and dogs to determine its level of toxicity and other factors. Bistrimate was then used on fifteen test subjects. It was determined that a potentially effective urinary excretion level could usually be maintained at a dosage which was well tolerated over extended periods. In two cases the drug had to be discontinued because of anorexia. Otherwise there were no evidences of toxicity. Five patients with syphilis, when treated with the new drug, showed the typical response of the effects of bismuth therapy. The authors concluded that Bistrimate affords a safe and convenient means of administration where bismuth is indicated. Sawicky[93] reported treating thirty cases of lupus erythematosus with this drug in doses of one to two tablets (75-150 mg. of metallic bismuth) three times a day. Some patients received the drug for as long as twenty-six weeks. Treatment had to be stopped in two cases who developed stomatitis with trigeminal neuralgia. Two other patients developed stomatitis but were able to continue on reduced dosage. One patient developed muscular pain in all four extremities, but after a two-week rest period he resumed treatment without ill effect. Blood and urine studies in all patients showed no significant abberations.

Quinacrine Hydrochloride (Atabrine)

Occasional reports on dermatitis due to atabrine continue to appear in the literature.[7,75] Nisbet[75] has comprehensively reviewed the subject in the light of his personal experience and also the voluminous literature on the subject. Atabrine principally produces three main types of cutaneous reactions. The eczematoid type is the most common reaction and accounts for about 80 per cent of cases of dermatitis from the drug. This is a chronic, dry or exudative, symmetric eruption occurring most frequently about the ears, eyelids, periorbital region, the dorsa of the hands and feet, and those areas most often affected by seborrheic dermatitis. The second type is lichenoid and constitutes about 12 per cent of patients affected. This type resembles lichen planus although it is more widespread. This has been the most publicized form of atabrine dermatitis. The third type of reaction is exfoliative dermatitis similar to that produced by arsenicals. It may be a primary reaction or secondary to the lichenoid or eczematoid types. Other untoward reactions include hepatic damage, visual disturbance, and psychosis. Barker[7] reported a case of hyperkeratosis of the palms and soles which he believed was caused by atabrine ingestion.

Miscellaneous Drug Eruptions

Five cases are reported by Watson et al[109] in which purpura followed the administration of stilbesterol or other estrogenic substances. The clinical symptoms were accompanied by a marked decrease in the platelet count. In the majority of the cases the estrogens had been administered over a prolonged period. The authors were guarded in their conclusions. They simply suggested that allergy to estrogens may be a factor in purpura inasmuch as there are a number of reports on the association of purpura with menstruation.

Fourteen patients, of whom thirteen were female, were studied by Bauer et al[9] following reactions after intramuscular injections of pork liver extract. These patients were found to be sensitive to pork, the sensitivity being species-specific rather than organ-specific. The most common reaction was urticaria with pruritus and edema of the face and lips. The second general type of reaction was manifested by cyanosis, perspiration, thready pulse, weakness, and fainting. Local swelling, induration, and pruritus at the site of injection was a third type of reaction. All symptoms disappeared with change to beef or lamb extracts.

Lima[60] reported the case of a thirty-three-year-old nondiabetic person with an atopic history who became sensitized to crystalline insulin. The reaction consisted of a generalized urticaria. Ophthalmic, scratch, and intradermal tests with crystalline insulin and with beef and pork regular insulin were positive. The same tests elicited negative results with beef and pork pancreatic extracts and with 1 per cent amylopsin solution. It was possible to demonstrate serum reagins for only crystalline insulin. Leavitt and Gastineau[58] showed in two insulin-sensitive diabetic patients that it was possible to reduce the intensity of the reaction either by prior oral administration of Benadryl or by the addition of Benadryl in 1:1000 solution directly to the insulin in the syringe.

Melkon and Scheidell[69] reported eight episodes (in six patients) of constitutional

anaphylactic-like reactions following the injection of sclerosing solutions into varicose veins. Such reactions have been reported previously. The patients developed urticaria, were warm and weak with rapid pulse, low blood pressure, and puffy congested eyes. Two of the episodes were produced by quinine HCl and urethane. The remainder were equally divided between sodium morrhuate and Sylnasol. The symptoms were the same regardless of the inducing agent. The reviewers have recently seen a case demonstrating such a reaction following repeated injection of sodium morrhuate into varicose veins. Recovery was complete in about half an hour following injection of 0.5 c.c. of 1:1000 adrenaline subcutaneously.

A case of exfoliative dermatitis due to codeine sensitivity has been reported by Moyer.[72] Drug eruptions due to codeine are extremely rare. Only twelve cases have previously been reported.

Rowe and Rowe[92] reported four cases of local necrosis (Arthus phenomenon) due to cutaneous allergy to extracted epinephrine. Three of the four patients subsequently used synthetic epinephrine without local reactions.

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RABIES VACCINE (ULTRAVIOLET IRRADIATION KILLED)

Brains of rabbits paralyzed by infection with fixed rabies virus are harvested, emulsified and brought to a 10 per cent by weight suspension of tissue in isotonic solution of sodium chloride and filtered through sterile bolting silk. Following filtration, the tissue suspension in a continuously flowing thin film is exposed to the germicidal rays of ultraviolet lamp. Preserved with sodium ethyl mercuri thiosalicylate 1:10.000. Rabies Vaccine (Ultraviolet Irradiation Killed) is employed for the prophylaxis of rabies.

Dosage.—1 c.c. subcutaneously, daily for 14 to 21 days. For severe exposure-bites on face or adjacent to central nervous system, 21 doses, two daily for the first three to seven days and then one dose daily. (J.A.M.A., 137: 1317, 1948)

News Items

ALLERGY INSTRUCTIONAL TOURS

The Committee on Extension of Postgraduate Education of the American College of Allergists (Chairman, Dr. Jonathan Forman) is attempting to arrange a series of instructional tours throughout the country. Each tour will consist of a number of cities which can be visited within a period of a week or two. Allergists in these cities will be asked to co-operate with the committee allowing themselves to be visited by out-of-town men for teaching purposes, not in the sense of formal undergraduate instruction but to enable the visitors to pick up what information they can. While the visitors will for the most part be practitioners who are not full-time allergists, there is no reason why allergists themselves should not take advantage of this program so as to allow for a mutually beneficial exchange of ideas and experiences.

Some allergists throughout the country have already been queried on the subject and almost without exception have agreed to take part in the program. A well-known laboratory on the West Coast has offered to participate by showing visitors techniques of pollen collection and extraction and specimens of the local flora, not only from their herbarium but also by visits to the field and to the pollen shed.

Present plans call for a central registry where a list of participants in this program will be kept and where itineraries will be planned for applicants. After the latter indicate which cities and which men they wish to visit, the allergists to be visited will be notified in advance as to who will visit them and when.

Fears of being flooded with tourists have been expressed by some men. The committee realizes the inconveniences accompanying intrusion on office or clinic time, and every effort will be made to minimize this. In the first place, the number of visitors seen by any one man will be sharply restricted to no more than possibly three or four a year, to begin with. Secondly, the time of stay will generally be no longer than one afternoon, possibly two. Thirdly, the qualifications of each applicant and the time of his visit will be sent to the co-operating allergist in advance. Should circumstances so dictate, the allergist will then have the opportunity of notifying the central bureau of his inability to accept the applicant, and the visitor will consequently not be routed to him. On the other hand, unless such occasions are truly exceptional, the purpose of the program could be easily negated, so that obviously only those physicians should take part in this program who are willing and able to accept the entailed burdens.

Preliminary response to the project has been heartening, and the Committee now desires to expand the scope of its plans. The co-operation of any member of either College or Academy, who desires to participate under the conditions outlined above, is invited. Also invited is the co-operation of dermatologists and ENT men who would be interested in furthering this program. All such physicians who have not been queried up to now and who clearly understand the potential demands which may be made upon their time are urged to send their schedule of office and clinic hours (together with comments on special and general facilities, if desired) to Dr. A. M. Targow, 6333 Wilshire Boulevard, Los Angeles 36, California.

COURSE IN CLINICAL ALLERGY

Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York, announces a course in Clinical Allergy under Dr. Robert A. Cooke and his staff at Roosevelt Hospital from November 8 through 20, 1948.

This course is designed to provide internists, pediatricians, and other physicians a review of modern concepts of the theoretical and practical aspects of allergy, in relation to clinical problems. All types of allergic disease will be studied including the less common vascular and cerebral allergies. The practical work will include history taking, physical examination, skin testing by direct and passive transfer methods, and laboratory diagnosis. In the laboratory the principles of allergic extractions and standardizations will be considered in a practical way and the preparation of individual extracts. There will also be demonstrations of anaphylaxis, Dale reactions, precipitin tests and preparation of autogenous vaccines. Maximum class, 8; minimum 6.

Those desiring to take this Course should write to Dr. John B. Truslow, Assistant Dean, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York.

PITTSBURGH ALLERGY SOCIETY

At the May meeting of the society the following program was presented:

1. A Report of the Pollen Commission—E. P. Claus, Ph.D., Chairman.
2. Streptomycin Sensitivity—Case report—J. A. Mansmann, M.D.
3. Kaposi's Varicelliform Eruption—Report of Two Cases—Irwin Solow, M.D. (guest).

SWISS ALLERGY SOCIETY

Word has been received that next month a new Swiss Allergy Society is to be organized. The most outstanding commercial and research workers in Switzerland are already members of the International Association of Allergists and they will sign an appeal to form a Swiss organization.

* * *

A copy of the Financial Report of the American College of Allergists for the year 1947 will be sent to any member of the College requesting it. Requests should be addressed to the Secretary-Treasurer, 423 La Salle Building, Minneapolis 2, Minnesota.

* * *

Word has been received from Dr. Donald G. Anderson, Secretary of the Council on Medical Education and Hospitals, that through an oversight in his office the listing of the Postgraduate Course to be given by the American College of Allergists, November 8-12, 1948, was not included in the listings of the June 19 issue of *The Journal of the American Medical Association,* but that a News Item concerning this course will be included in an early issue of *The Journal.* Our instructional courses have been listed in the past under the Postgraduate Continuation Courses for Physicians compiled by the Council on Medical Education and Hospitals.

* * *

Dr. Bernard N. Halpern, Paris, France, the Lauréat of the Institute and Academie of Medicine, Chief of Laboratories of the Faculté of Medicine and Chief of Research of the National Center of Scientific Research, is coming to America in September. Dr. Halpern is especially noted for his contributions on the antihistaminic drugs. He plans to visit Chicago, then the Mayo Clinic and return to New York where he will give two lectures at the Blumenthal Auditorium of the Mt. Sinai Hospital under the auspices of The American College of Allergists: On October 7, 8:30 p.m., "The Role of the Capillary Permeability in the Production of Acute Pulmonary Edema and the Action of the Synthetic Antihistaminic Substances in this Syndrome," and on October 14, 8:30 p.m., "Experimental and Clinical Researches on a New Series of Antihistaminic Substances Derived from Phenothiozine." All physicians interested, particularly allergists, are invited to attend these lectures.

QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY

Recently new appointments have been made to the Editorial Board of the *Quarterly Review of Allergy and Applied Immunology*. The Editorial Board now consists of Fred W. Wittich, M.D., Editor-In-Chief, Harold A. Abramson, M.D., Ethan Allan Brown, M.D., Stephan Epstein, M.D., Jerome Glaser, M.D., French K. Hansel, M.D., David Harley, M.D., Bayard T. Horton, M.D., Werner Jadassohn, M.D., Paul Kallos, M.D., A. Oliveira Lima, M.D., Harry C. Olislagers, M.D., Bret Ratner, M.D., G. Estrada de la Riva, M.D., Adolph Rostenberg, Jr., M.D., Guido Ruiz-Moreno, M.D., Prof. Dr. Piero Sangiorgi, Morris Scherago, D.V.M., Albert V. Stoesser, M.D., J. Warrick Thomas, M.D., and Alfred J. Weil, M.D.

THE INTERNATIONAL ASSOCIATION OF ALLERGISTS

A full page advertisement will appear in THE ANNALS soon announcing the publication of the *International Archives of Allergy and Applied Immunology*, the official organ of the International Association of Allergists. The first issue will consist of a symposium on psychosomatic and neurologic allergy. The Editorial Board, composed of some of the most outstanding scientists throughout the world, will soon be completed.

Provisional plans have been made to hold the first International Congress at Zurich in October, 1949. Professor William Löffler of Zurich is Chairman of the Congress and Professor A. Grumbach of Zurich is the General Secretary. A tentative program has been arranged and the persons to be invited as reviewers and lecturers have been selected. Professor Rolf Meier of Basel, Switzerland, has invited the members of the International Association to spend at least one day of the Congress at Basel where the pharmacologic aspects of the allergic diseases will be discussed in connection with demonstrations by the large chemical industries there. A registration of at least 400 is anticipated.

FORUM ON ALLERGY

A forum on Allergy will be held under the auspices of the Central Pennsylvania Allergy Society in the Luzerne County Medical Society Building, 130 South Franklin St., Wilkes-Barre, Pennsylvania, Thursday, October 14, 1948.

A business meeting and luncheon for members of the Society will be held at Hotel Sterling in the morning.

The afternoon program will include the following scientific papers, with discussion after each paper.

"Food Allergy"—ARTHUR C. KALISCH, M.D.

"The Treatment of Asthma from the Viewpoint of a General Practitioner"—HARRY L. ROGERS, M.D.

"Papular Urticaria"—JOHN P. SCULLY, M.D.

"The Present Status of Antihistamine Drugs"—MERLE M. MILLER, M.D.

"Office Management of the Allergic Child"—JEROME GLASER, M.D.

"Bronchoscopy as Applied to Allergy"—SAMUEL T. BUCKMAN, M.D.

Special exhibits will be on display. Following the scientific session dinner will be served in the Adams Room, Hotel Sterling, and will be open to physicians, members, wives and friends. Reservations should be made through the Secretary-Treasurer, Ralph M. Mulligan, M.D., 18 North Eleventh Street, Reading, Pennsylvania.

DRUG FIRM AWARDED CITATION BY NAVY FOR WAR WORK

Award of a certificate of achievement to Winthrop Chemical Company, now Winthrop-Stearns, Inc., manufacturer of pharmaceuticals, was made July 15, 1948, by the Surgeon-General, U. S. Navy, in recognition of "Meritorious and outstanding services rendered to the Navy's Medical Department during World War II."

IN MEMORIAM

CLARENCE K. WEIL, M.D., F.A.C.A.

As the ANNALS OF ALLERGY was going to press, we were shocked when receiving the sad news of the sudden death of Dr. Clarence K. Weil of Montgomery, Alabama, in May, 1948, at the age of forty-eight years. Dr. Weil was born May 16, 1900, in Montgomery. He was graduated from Starke's University School in 1916 and from the University of Alabama, receiving the degree of B.S., in 1919. He was graduated from Columbia University Medical School in 1923 and held an internship at Mt. Sinai Hospital in New York from 1923 to 1926.

Doctor Weil was an instructor of nurses at St. Margaret's Hospital in Montgomery. He was also an instructor of residents at St. Margaret's Hospital.

Doctor Weil was a member of Phi Beta Kappa and Alpha Omega Alpha honorary societies, and a member of The American Academy of Allergy and The American College of Allergists. He was also a member of the American College of Physicians and was certified by the American Board of Internal Medicine.

Doctor Weil, at the time of his death, was Chief of Staff of the Medical Service at St. Margaret's Hospital, and Chairman of the Hospitalization Committee. He belonged to the Montgomery County Medical Society and the Alabama State Medical Society. Doctor Weil served with distinction in both World War I and World War II with the rank of Lieutenant Colonel.

Doctor Weil made some valuable contributions to the field of medicine, and allergy in particular. He studied assiduously the local problems which may be factors in causing hay fever in Alabama. He published work on plants causing hay fever in Alabama, and he is particularly known for his article on "Summer Hay Fever of Unknown Origin in the Southeast," which appeared in the *Journal of Allergy*, May, 1940. He thus pioneered the recognition of the hay fever "x" problem in the South, which has been the subject of much investigation by himself and his colleagues.

Doctor Weil is survived by his wife, Dorothy, and two daughters, Mrs. Lee Rudlin and Miss Joan Weil.

The officers and members of the College extend their deepest sympathy to the immediate family.

OPPORTUNITY FOR JUNIOR FELLOW

A well-known allergist with an established allergy practice is desirous of adding to his staff a junior fellow to study and profit by the many cases of all types of allergic manifestations that pass through his private office and those encountered in the free clinics in which he is connected. The maximum compensation of $150.00 a month would be available, providing the applicant would agree to stay a minimum of six months up to a maximum of one year. Application together with photograph and qualifications and recommendations from two or three recognized internists or allergists, should be addressed to The American College of Allergists, 423 La Salle Medical Bldg., Minneapolis 2, Minnesota.

A Post-Convention Suggestion

The May-June issue of the ANNALS OF ALLERGY featured a trip over the Northern Pacific Railway through Minnesota, North Dakota, Montana, Idaho, and Washington for those planning to attend the American College of Allergists Instructional Course to be held in Portland, Oregon, November 8 to 12, 1948. Supplementing this suggestion, we are pleased to show below a suggested return itinerary including a side trip via steamer from Seattle to Victoria and sight-seeing trips in these interesting seaports.

Lv. Portland—Nor. Pac. Ry	11:30 PM	Nov. 8
Ar. Seattle—Nor. Pac. Ry.	6:30 AM	Nov. 9
Lv. Seattle—Can. Pac. Steamer	7:50 AM	Nov. 9
Ar. Victoria—Can. Pac. Steamer	12:50 PM	Nov. 9
Tour this very interesting Canadian Capital City and the exotic Butchart's Gardens.		
Lv. Victoria—Can. Pac. Steamer	4:30 PM	Nov. 9
Ar. Seattle—Can. Pac. Steamer	9:30 PM	Nov. 9
Overnight in Seattle.		
Open Forenoon.		
2:00 PM—Tour business, financial, residential and University districts of this interesting city and seaport. Two full hours of comprehensive sightseeing.		
Lv. Seattle—North Coast Limited	10:45 PM	Nov. 10
Spokane—North Coast Limited	8:15 AM	Nov. 11
Lake Pend Oreille, Cabinet Gorge and Mission Range.		
Missoula	3:35 PM	Nov. 11
Hell Gate Canyon.		
Butte	6:20 PM	Nov. 11
Biggest mining camp on earth, Continental Divide, Bozeman Pass.		
Livingston	10:25 PM	Nov. 11
Absaraka Mountains and Yellowstone River.		
Bismarck	12:20 PM	Nov. 12
Capital of North Dakota, Missouri River, Red River Valley—Breadbasket of the world.		
Fargo		
Minnesota—Land of 10,000 Lakes		
Minneapolis	9:27 PM	Nov. 12
St. Paul	10:00 PM	Nov. 12
Chicago	7:50 AM	Nov. 13

The return portion of your ticket may be routed via the Northern Pacific and at Seattle side trip to Victoria will be provided without charge. Sightseeing at Victoria $1.73; Seattle $2.30, including tax; Hotel cost about average. Apply to any Northern Pacific Agent or your Local Ticket Agent.